"HYPONATREMIA IN STROKE: CEREBRAL SALT WASTING VERSUS SYNDROME OF INAPPROPRIATE ANTI-DIURETIC HORMONE SECRETION"

conducted at

COIMBATORE MEDICAL COLLEGE

Submitted in partial fulfillment of the requirements
for the award of the degree

M.D. GENERAL MEDICINE

BRANCH -1

to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATES

CERTIFICATE

Certified that this is the bonafide dissertation done by ***Dr. MITHRA PRASAD*** *from July 2014 to June 2015 during the academic year 2013 to 2016 and submitted in partial fulfillment of the requirements for the Degree of* ***M.D.,General Medicine****, Branch I of* ***The Tamil Nadu Dr. M.G.R. Medical University, Chennai.***

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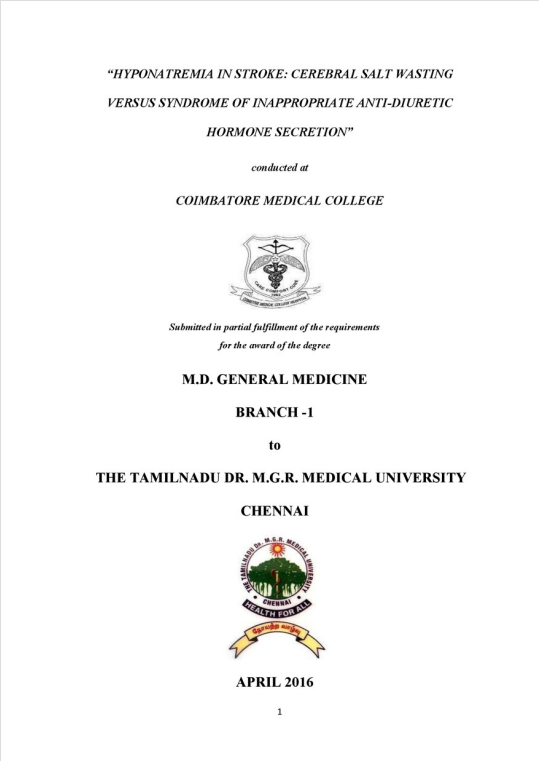

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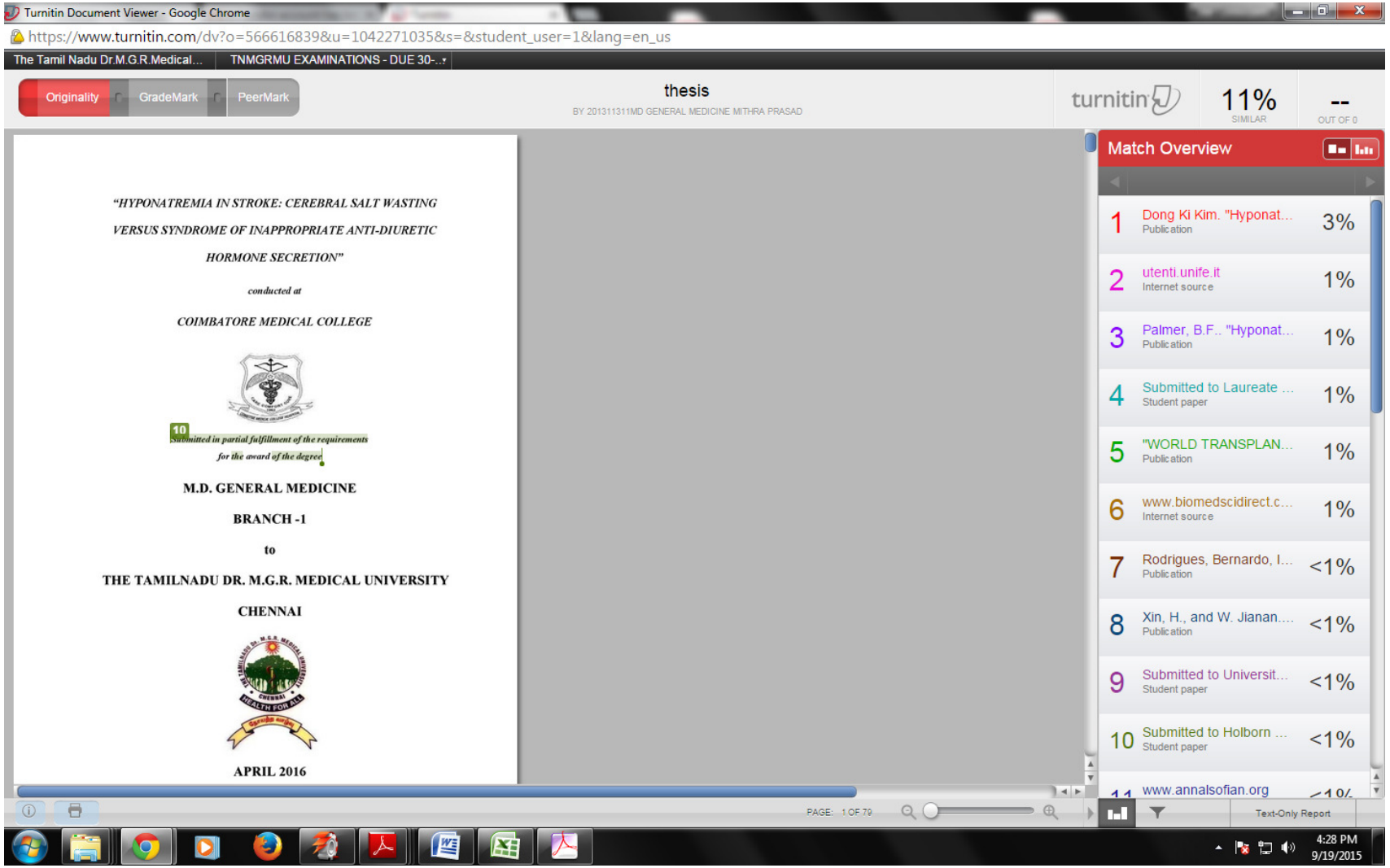
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DECLARATION

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I solemnly declare that this dissertation entitled *"Hyponatremia in stroke: Cerebral Salt Wasting versus Syndrome of Inappropriate Anti-Diuretic Hormone secretion"* bonafide and genuine research work carried out by me at Coimbatore Medical College and Hospital, from July 2014 to June 2015, during the academic year 2013-2016, under the guidance and supervision of **Dr. KUMAR NATARAJAN,MD.,** Professor, Department of Medicine, Coimbatore Medical College Hospital, Coimbatore.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University, towards the partial fulfilment of requirement for the award of M.D.Degree in General Medicine (Branch-I).

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Date: **Dr. MITHRA PRASAD**

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MITHRA PRASAD

LIST OF ABBREVIATIONS

SIADH	–	Syndrome of inappropriate Anti-Diuretic Hormone secretion
CSW	-	Cerebral Salt Wasting
AVP	-	Arginine Vasopressin
BUN	-	Blood Urea Nitrogen
RTA	–	Renal Tubular Acidosis
ECF	-	Extra-Cellular Fluid
ICF	–	Intra Cellular Fluid
MDMA	–	Methylene-dioxy Methamphetamine
TURP	–	Trans Urethral Resection of Prostrate
CSF	-	Cerebro Spinal Fluid
SAH	-	Sub Arachnoid Hemorrhage
EABV	-	Effective Arterial Blood Volume
BNP	-	Brain Natriuretic Peptide
RAS	–	Reticular Activating System
GFR	-	Glomerular Filtration Rate
ADH	–	Anti Diuretic Hormone

ICH	-	Intra Cerebral Hemorrhage
CT	-	Computed Tomography
MRI	–	Magnetic Resonancce Imaging
DW MRI	-	Diffusion Weighted MRI
PET	-	Positron Emission Tomography
SPECT	-	Single Photon Emission Computed Tomography
rtPA	–	Recombinant Tissue Plasminogen Activator
VKA	–	Vitamin K Antagonist
Glu	-	Glucose
Na	-	Sodium
K	-	Potassium
Cl	-	Chloride
TBW	-	Total Body Water
SSRI	–	Selective Serotonin Reuptake Inhibitors
TCA	–	Tricyclic Antidepressants
NSAID	-	Non Steroidal Anti-Inflammatory Drugs
ACA	–	Anterior Cerebral Artery
MCA	–	Middle Cerebral Artery
PCA	–	Posterior Cerebral Artery

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INTRODUCTION

INTRODUCTION

Hyponatremia is the most common electrolyte abnormality seen in hospitalised patients and is also the most common electrolyte imbalance seen in critically ill neurologic patients. It can significantly alter the morbidity, short and long term mortality of the underlying disease.

The causes of hyponatremia are varied, but in neurologically ill patients, are most commonly attributed to Syndrome of Inappropriate Anti-diuresis and Cerebral Salt Wasting. Both these entities are cerebral in origin but have distinct pathophysiology, prognosis and treatment options. The importance of distinguishing both lies in the fact that the therapy indicated for one if used for the other, can be deleterious.

Distinction between the two requires a battery of investigations since there is considerable overlap between the two conditions, and no single parameter can define either entity.

SIADH is a subclinically volume expanded state due to inappropriate anti-diuresis. This causes excessive volume overload over the body sodium content leading onto euvolemic hyponatremia. In stroke SIADH occurs due to AVP secretion inappropriate to the osmotic threshold. The suppressed proximal renal tubular transport in this condition can lead on to bicarbonaturia and hypouricemia. The effective treatment is fluid restriction. Hypertonic saline therapy is reserved for cases of severe hyponatremia.

CSW, on the other hand, is essentially a volume depleted state, which occurs due to the combined effects of decreased sympathetic outflow and increased natriuretic peptides. This resultant natriuresis leads to volume depletion and an appropriate AVP response. So the treatment for CSW includes an aggressive volume replacement regimen with isotonic saline or in severe cases, hypertonic saline.

Thus most CSW patients meet the criteria for SIADH and have elevated AVP levels but worsen with the treatment protocol given for SIADH. This observation lead to the description of CSW as a separate entity and widespread studies were carried out to distinguish the two entities.

At present the two entities are differentiated using combined analysis of sodium levels, plasma osmolality, uric acid, effective arterial blood volume, urine sodium, serum potassium, haematocrit, BUN/creatinine ratio.

Hyponatremia, especially Cerebral Salt Wasting, occurring in the setting of stroke has been shown to worsen the prognosis of stroke, increase morbidity, short and long term mortality, and cause a poorer discharge disposition.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

- To study the prevalence of hyponatremia in the setting of acute stroke

- To distinguish between SIADH and CSW among hyponatremic patients

- To study the implication of SIADH and CSW on the short term outcome of stroke.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The consequences of salt depletion was first described by Mc Cance in 1936 [1].

In 1950, Peters et al [2] at Yale described three neurologic patients with hyponatremia. Both patients had increased urine sodium loss and dehydration in spite of high sodium diet. In 1952, Cort [3] in Yale described another similar patient as having Cerebral salt wasting syndrome.

In1953,Leaf et al[4] demonstrated that giving exogenous vasopressin caused hyponatremia and natriuresis. He described this to be a physiologic response to increased intra-vascular volume.

Schwartzet al [5] published the paper on SIADH which became a milestone. For over two decades the term CSW vanished from literature. In 1981,Nelson et al [6] reintroduced the term based on his findings in patients with sub-arachnoid haemorrhage, finding volume contraction in those patients in spite of hyponatremia.

Further correlations between hyponatremia in subarachnoid haemorrhage with increased levels of natriuretic peptides, negative sodium balance,[7], [8] and low central venouspressure[9] were published.

SODIUM AND WATER REGULATION

The interactions between the kidney and the brain play an important role in the sodium and water homeostasis.

Arginine vasopressin or the Anti-diuretic hormone is the key hormone and is synthesised in a precursor form in the magnocellular neurons of the supra-optic and paraventricular nuclei in the hypothalamus. From the hypothalamus it is transported by axonal transport to the neurohypophysis in the pituitary and is cleaved to the active form and secreted into the blood.

Disorders of sodium balance are due to disorders in regulation of water balance. Defects in water intake and Arginine vasopressin levels are the major effectors of plasma osmolality. This would in turn affect the sodium levels.

HYPONATREMIA

Hyponatremia is the most common electrolyte disturbance in neurologic patients [10]Hyponatremia is defined as sodium level of less than 130 meq/L and occurs in 20% of hospitalised patients [11] and the in-hospital mortality rate is found to be 1.5 fold higher than those with normal sodium levels [12].

Water and sodium homeostasis are tightly regulated and thus disturbances in water homeostasis can lead onto sodium imbalance.

Sodium being the major extracellular ion is the principal determinant of serum osmolality. Thus the interplay between circulating vasopressin and water intake plays a key role in regulating the serum osmolality. Relative sodium concentration thus changes with water homeostasis and hence absolute plasma sodium values do not suffice to tell about the volume status of the patient. Hyponatremia is a very common disorder occurring in upto 22% of inpatients.

The main mechanisms responsible include

1) Increase in circulating Vasopressin
2) Increased renal sensitivity to AVP
3) Low solute intake

Based on the underlying pathophysiology, hyponatremia may be Euvolemic, Hypovolemic or Hypervolemic

HYPOVOLEMIC HYPONATREMIA

Hypovolemia

↓

Neurohumoral activation

↓

Increased circulating Vasopressin levels

↓

1) V1A receptor mediated blood pressure maintenance
2) V2 receptor mediated free water reabsorption

Hypovolemic hyponatremia may be caused through

1) Renal losses like RTA, diuretic usage, ketonuria, osmotic dieresis and rarely cerebral salt wasting syndrome.In renal losses, there is excessive loss of solute from the body and hence an appropriate rise of circulating AVP occurs. Salt losing nephropathies typically lead to hyponatremia in the setting of a reduced sodium intake. Causes of salt losing nephropathies include reflux nephropathy, medullary cystic disease, post-obstructive uropathy and the recovery phase in Acute Tubular Necrosis.

Thiazide diuretics cause not only diuretic induced volume depletion but can also cause polydipsia. Increased excretion of an osmotically active agent like ketonuria, glycosuria, mannitol administration and bicarbonaturia.

2) Non- renal losses like third space fluid loss like pancreatitis, GI losses like vomiting or diarrhoea, insensible loss like burns

In renal losses, urinary sodium measures > 20 mM whereas in non renal losses the urinary sodium tends to remain < 20 mM.

HYPERVOLEMIC HYPONATREMIA

This is characterised by an increase in the the total body sodium content and an inappropriately greater increase in the total body water. The different causative mechanisms can be differentiated by the urinary sodium concentration with acute or chronic renal failure causing increased urinary sodium, and cirrhosis, cardiac failure causing decreased urinary sodium excretion. The degree of hyponatremia serves as an indirect measure of the degree of neuro-humoral activation and hence serves as an important prognostic factor.

EUVOLEMIC HYPONATREMIA

Conditions leading onto increased total body water in the setting of a normal sodium concentration result in euvolemic hyponatremia.

Causes of euvolemic hyponatremia:

1) Moderate to severe hypothyroidism which is corrected once euthyroid state is achieved
2) Pituitary disease causing secondary adrenal insufficiency due to a predominant glucocorticoid deficient state. In contrast, primary adrenal insufficiency, causing aldosterone deficiency, leads on to hypovolemic hyponatremia.

   Glucocorticoids exert a negative feedback on vasopressin release in such an effective manner, that hydrocortisone replacement can rapidly normalise the circulating AVP, correcting the sodium imbalance.
3) The Syndrome of Inappropriate Anti-diuresis is the most frequent cause of euvolemic hyponatremia. In SIADH the osmotic threshold and the osmotic response curves are shifted downward. The precipitation of hyponatremia is by excessive free water intake at serum osmotic values lesser than the normal threshold.

Patterns of SIADH-

Four distinct patterns of SIADH are known to occur

1) Unregulated erratic AVP secretion- seen in one-third of the patients, where the AVP secretion does not correlate with the serum osmolality.
2) Failure of suppression of AVP secretion at lower serum osmolalities with a normal response to hyperosmolar conditions.

3) Resetting of the osmostat – causing lowering of the osmotic threshold and left shift of the osmotic response curve.

4) Gain in function of renal water reabsorption or a circulating anti-diuretic substance apart from vasopressin. A gain of function mutation of the V2 AVP receptor in the collecting tubule has been described. This could lead to constitutive activation of the V2 AVP receptor even in the absence of AVP and hence leads on to Nephrogenic SIADH.

SIADH patients are not euvolemic but have a subclinically expanded body volume. This volume expansion is due to vasopressin mediated water and sodium chloride retention. In SIADH, there is increased distal sodium and water transport and this leads to a supressed proximal tubular reabsorption and thus leading to low serum uric acid levels (<4 mg/dl), in contrast in patients with hypovolemic hyponatremia, there is hyperuricemia due to shared activation of proximal tubule sodium-chloride and urate transport.SIADH is caused by a variety of diseases, the common causes of which include pneumonia, tuberculosis, pleural effusion, tumor, subarachnoid haemorrhage, meningitis. It can also occur as a para-neoplastic condition as in small cell carcinoma of the lung, attributing to 75% of the malignancy associated SIADH. Upto 10% of the patients with this tumor are found to have sodium levels of< 130mM during initial presentation.

SIADH is also frequently caused by drugs like Selective Serotonin Reuptake Inhibitors.

Other drugs can cause SIADH by causing enhanced sensitivity to the circulating vasopressin, and they include

Chlorpropamide

Tricyclic antidepressants

Clofibrate

Carbamazepine

Vincristine

Nicotine

Narcotics

Ifosfamide

MDMA- can cause acute hyponatremia

Desmopressin

Oxytocin

Vasopressin

Hyponatremia due to low solute intake-

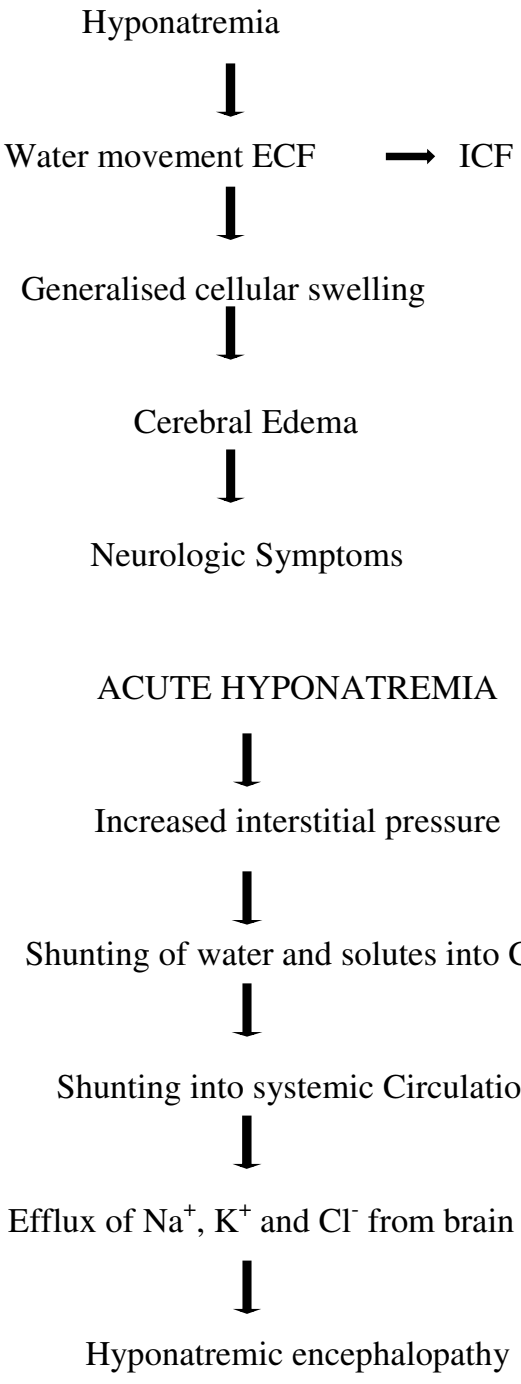
Commonly seen due to beer potomania, beer having a low salt and protein content (1-2mM of sodium) and excessive beer intake can caue hyponatremia.

It has also been described in people eating extreme vegetarian diets and other nutrient restricted diets.

These patients typically present with a very low urine osmolality (< 100-200 mOsm/kg) and a urine sodium of < 10-20 mM. The reduced urinary

sodium excretion will also limit water excretion thus causing volume expansion and thus hyponatremia occurs in the setting of modest polydipsia. Resumption of a normal diet rich in solute or saline hydration would correct the hypovolemia due to low solute intake.

CLINICAL FEATURES OF HYPONATREMIA



Acute hyponatremia is a medical emergency and can result in normocapneic or hypercapneic respiratory failure, seizures, brain stem herniation, coma and death.

CAUSES OF ACUTE HYPONATREMIA

Iatrogenic- post operative

Hypotonic fluid therapy causing increased AVP

Glycine irrigation- during TURP/ Uterine surgery

Colonoscopy Preparation

Recent thiazide use

Polydipsia

MDMA intake

Exercise

Multifactorial causes

CHRONIC HYPONATREMIA

Chronic persistent hyponatremia

↓

Efflux of organic osmolytes from brain cells

↓

Decreased intracellular osmolality

↓

Water influx down the osmotic gradient into the cells

Chronic hyponatremia can still result in some amount of nausea, vomiting, confusion, and seizures especially when levels fall below 125mM

At times the patient may manifest only with subtle gait defects, increased fall risk and cognitive defects that are reversible with sodium correction.

During correction of hyponatremia, the the re-accumulation of the brain osmolytes as the osmolality rises is delayed and this could result in degeneration of oligodendrocytes and hence demyelination. This is especially marked during rapid correction and there is also a disruption of the blood brain barrier and entry of immune mediators, contributing to the demyelination. The classical region affected is pons where the re-accumulation of osmolytes is markedly delayed. Clinically, the patients may present after 1 or more days with paraparesis, quadriparesis, ‘locked-in syndrome’ or coma.

Approach to a neurologic patient with hyponatremia

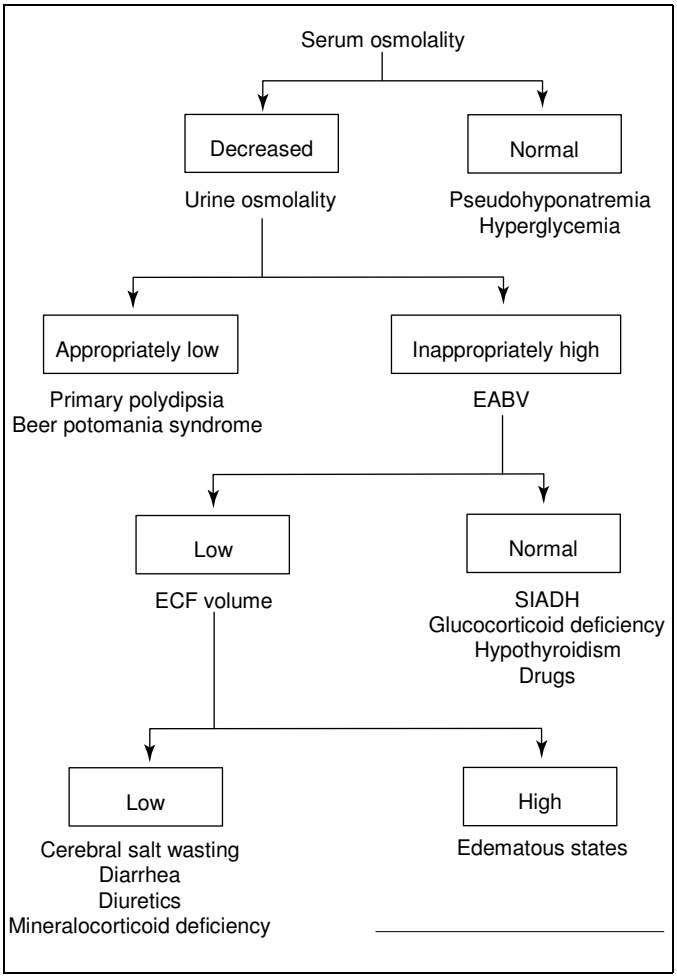


Fig.1 THE GENERAL APPROACH TO THE HYPONATREMIC PATIENT

Cerebral salt wasting (CSW) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) can be differentiated most effectively by assessment of the volume status of the patient.

Abbreviations: ECF, extracellular fluid volume; EABV, effective arterial blood volume.

Hyponatremia in the setting of central nervous system diseases occur commonly in two patterns-

1. Syndrome of Inappropriate Anti- Diuretic Hormone secretion and

2. Cerebral Salt Wasting

due to interaction between the brain and kidneys [21]

SYNDROME OF INAPPROPRIATE ANTI- DIURETIC HORMONE SECRETION

SIADH is a volume-expanded state

In SIADH, there is

1) Inappropriate increase in ADH secretion which leads to an increased EABV.

2) downward resetting of the osmotic thirst threshold

leading on to a volume expanded state

As shown by studies of exogenous pitressin administration [4] to normal population, excess of vasopressin increases water retention and thus leads to an abrupt decrease in urine volume and increased urine osmolality, and leads to an increase in body weight and hyponatremia.

After several days, a steady state is reached and sodium excretion becomes equal to dietary sodium intake. This is attributed to the vasopressin escape phenomenon [22] causing decreased proximal sodium reabsorption.

During this steady state, large isotonic sodium load could lead to a quantitatively similar urinaryexcretion of sodium. [23] This shows that a normal renal handling in spite of decreased serum sodium is a characteristic in SIADH.

In SIADH, ECF expansion is not accompanied by overt signs of hypervolemia like neck vein distension or peripheral edema, but has increased GFR and increased renal blood flow. Due to decreased proximal tubular reabsorption, uric acid and urea, both of which are proximally reabsorbed, are also seen to decrease in blood [24]

Essential feature

Decreased effective osmolality (<275 mOsm/kg of water)

Urinary osmolality >100 mOsm/kg of water during hypotonicity

Clinical euvolemia

No clinical signs of volume depletion of extracellular fluid

No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes

No clinical signs of excessive volume of extracellular fluid No edema or ascites

Urinary sodium >20 mEq/L with normal dietary salt intake

Normal thyroid and adrenal function

No recent use of diuretic agents

Plasma uric acid <4 mg/dL

Blood urea nitrogen <10 mg/dL

Fractional sodium excretion >1%; fractional urea excretion >55%

Failure to correct hyponatremia after 0.9% saline infusion

Correction of hyponatremia through fluid restriction Abnormal result on test of water load (<80% excretion of 20 mL of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water)

Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia

FIG 2- DIAGNOSTIC CRITERIA FOR SIADH [25]

Encephalitis (viral or bacterial)	Cavernous sinus thrombosis
Meningitis (viral, bacterial, tuberculosis, fungal)	Neonatal hypoxia
Traumatic brain injury	Hydrocephalus
Brain abscess	Delirium tremens
Brain tumors	Cerebrovascular accident
Guillain-Barré syndrome	Acute psychosis
Acute intermittent porphyria	Peripheral neuropathy
Subarachnoid hemorrhage	Multiple sclerosis
Subdural hematoma Cerebellar and cerebral atrophy	Any kind of surgery, most notably transsphenoidal pituitary surgery

Fig 3- NEUROLOGIC DISEASES COMMONLY ASSOCIATED WITH SIADH

CEREBRAL SALT WASTING

The recognition of a distinct subset of hyponatremic patients having hypovolemia in spite of meeting the criteria of SIADH, lead to the discovery of Cerebral Salt Wasting. Wijdicks et al. [26] showed the development of a condition similar to SIADH in SAH patients but had a 10% decrease in plasma volume. He also found that a negative sodium balance preceeded the condition.

Levine et al. [27] showed hyponatremia and volume depletion in ten craniosynostosis post- operative patients in spite of intravenous fluid administration to match sodium output.

CSW is a volume-depleted state hypothesised to be due to decreased sympathetic nervous system outflow in patients with a CNS insult. Also shown to be implicated are increased levels of natriuretic factors like atrial natriuretic peptide and brain natriuretic peptide.

Pathophysiology of CSW

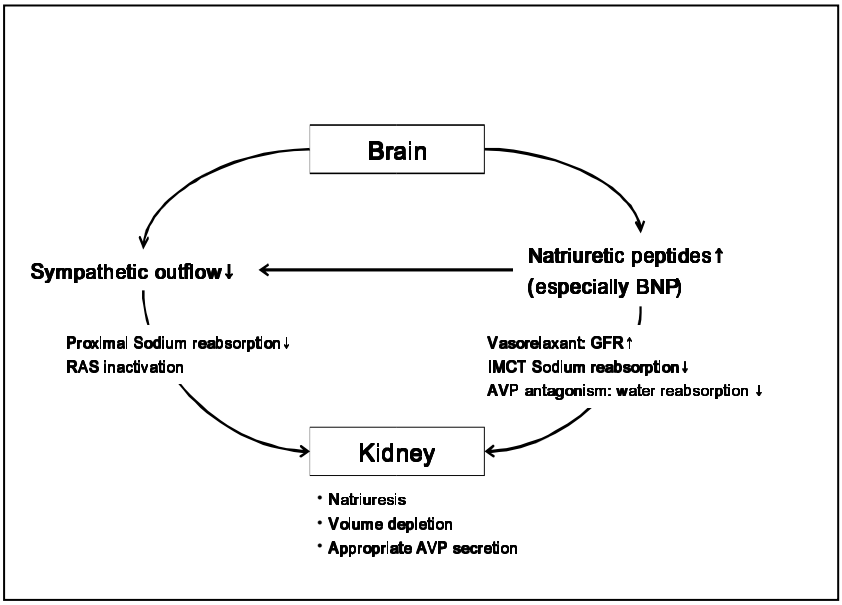


Fig 4. PATHOPHYSIOLOGY OF CEREBRAL SALT WASTING SYNDROME.

BNP, brain natriuretic peptide; RAS, rennin angiotensin system; AVP, Arginine vasopressin; GFR, glomerular filtration rate

Decreased sympathetic input to the kidney causes

1) Alteration in the sodium and water handling of the proximal tubule
2) Failure of rise in renin and aldosterone levels in response to hyponatremia[28, 29]

Increased natriuretic peptides can

1) Increase GFR by dilatation of afferent and constriction of efferent renal arterioles
2) Cause direct inhibition of sodium reabsorption from inner medullary cortical duct [30]

3) Direct inhibition of renin release in the juxta glomerular apparatus
4) Inhibition of aldosterone release from the adrenal glands
5) Decrease sympathetic outflow from the brain stem

Increased natriuretic peptides especially BNP has been proved by Berendes et al [29].Patients with SAH who underwent aneurysmal clipping were compared with controls of patients undergoing craniotomy for brain tumor resection. After a three to four day duration, the SAH group had a peak increase of urine sodium excretion and correlated with increased BNP levels. The BNP levels also correlated with intracranial pressure and with the level of urine sodium excretion.

The volume depletion in CSW activates baroreceptors thereby stimulating increased Anti-diuretic hormone secretion and hence patients with CSW also show increased ADH levels.

The incidence is found to be 34% in aneurysmal SAH patients [13] and 70% in tuberculous meningitis [14] and 35.3% in stroke[15] and 25-35% after trans sphenoidal surgeries [16, 17]

DIFFERENCES BETWEEN SIADH AND CSW

Differentiating between the two entities is of utmost importance due to the varied prognostic and treatment options between them.

Differentiation can be difficult due to an overlap of laboratory parameters between the two entities.

The primary difference lies in the effective arterial blood volume (EABV), which is increased in SIADH and vice versa in CSW. Since EABV is a clinical entity it can only be indirectly measured by levels of urine sodium excretion and ECF volume. Thus the differentiation of SIADH and CSW requires a panel of physical and laboratory investigations.

Physical features:

SIADH shows features of normal to increased ECF volume whereas

CSW shows dry skin and mucosa , orthostasis, flat neck veins, and a negative fluid balance [11]

Laboratory features:

	CSW	SIADH
Extracellular fluid volume[b]	Decreased	Increased
Hematocrit	Increased	Normal
Plasma albumin concentration	Increased	Normal
Plasma BUN/creatinine	Increased	Decreased
Plasma K[þ]	Normal or increased	Normal
Plasma uric acid	Decreased	Decreased
Treatment	Normal saline	Fluid restriction

Fig 5. DIFFERENTIATION BETWEEN SIADH AND CSW [11]

Determination of extracellular fluid volume is the primary way to differentiate CSW from SIADH.

Serum uric acid is a special tool in SIADH and CSW differentiation. It initially tends to be low in both [31, 32], being inappropriately low in CSW. On correction of sodium levels, it tends to normalise in SIADH whereas it remains abnormally low in CSW patients [31] due probably to prolonged proximal tubule dysfunction [31,33]

TREATMENT OF SIADH vs CSW

The treatment modalities widely vary for SIADH and CSW and it is important to distinguish between the two since inappropriate treatment can result in an adverse outcome.

In CSW, fluid restriction can worsen the already volume depleted state and can worsen the underlying neurologic problem.

Wijdicks et al. [34] showed the development of delayed cerebral infarction in 21 on 44 SAH patients who were treated with fluid restriction though 15 of these patients satisfied SIADH criteria. This was later attributed to possible CSW. The decreased plasma volume in conjunction with the vasospasm in SAH could have been the causative of delayed cerebral infarction.

Thus in CSW aggressive salt and fluid replacement is necessary to maintain intravascular volume

Intravenous saline (isotonic or hypertonic), salt tablets or agent with mineralocorticoid activity like fluodrocortisone are the various treatment options [35, 36]

On the other hand, SIADH requires fluid restriction as the treatment.

Intravenous saline given in this volume-expanded state could lead to symptomatic hyponatremia, and worsening clinical condition.

So the osmolality of the administered fluid should exceed the osmolality of urine [11].

More targeted therapies would include AVP receptor antagonists [37]

The other treatment options would include drugs like frusemide, demeclocycline and lithium.

Patients with acute sodium reductions and severe neurologic symptoms may need initial rapid sodium correction with hypertonic saline, but caution is necessary to prevent against osmotic demyelination during correction [38,39]

CEREBROVASCULAR ACCIDENT

Stroke is the second leading cause of death worldwide. The number of deaths due to stroke was 6.2 million in 2011.The number of stroke cases is projected to increase as the elderly population grows.

Stroke is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. Thus stroke is a clinically defined entity,

brain imaging and laboratory tests serving to be supportive to the diagnosis.The complex brain structure and vasculature are the reasons for the wide variability of clinical manifestations.

ISCHEMIC STROKE

A reduction of perfusion lasting longer than a few seconds suffices to cause cerebral ischemia, and overt neurologic symptoms manifest.This is mainly attributable to absent glycogen stores in the brain tissue. A cessation of blood flow lasting in minutes can cause brain infarction. A quick restoration of blood flow can cause full recovery of brain tissue and thus only transient symptoms, thus leading onto transient ischemic attack. Stroke is defined to have occurred when neurologic symptoms persist for more than 24 hours or if there is imaging evidence of infarction

A generalised blood flow compromise due to systemic hypotension can initially cause syncope. Persistent hypotension causes infarction at the borderline areas between the major blood vessel territories, called water-shed infarcts.

In more severe cases, global hypoxia- ischemia can result in diffuse brain injury and hypoxic ischemic encephalopathy.

Focal ischemia results from thrombosis or emboli in the arteries.

Intracranial haemorrhage is caused by bleeding into the brain parenchyma or in the surrounding region. The symptoms in hemorrhagic stroke

can result from mass effect of the surrounding structures or due to toxic effects of the blood or due to increasing intracranial pressure.

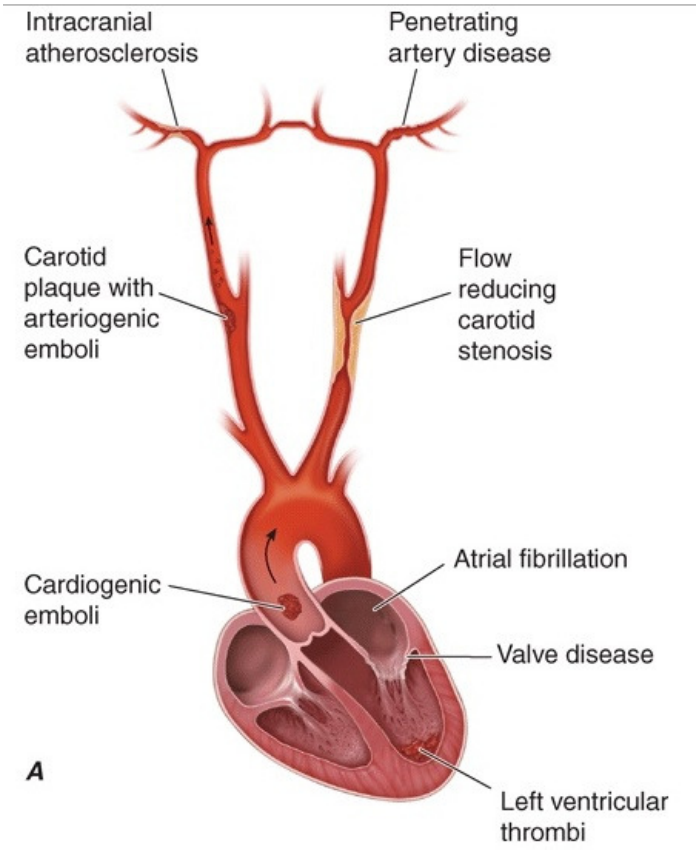


Fig 6. CAUSES OF ISCHEMIC STROKE

PATHOPHYSIOLOGY OF ISCHEMIC STROKE:

Occlusion of a cerebral blood vessel causes reduction in the regional blood flow.

The magnitude of blood flow reduction would depend on the extent of collateral blood flow. The reversible ischemic region surrounding a core area of infarction is called the ischemic penumbra which can be imaged by a perfusion- diffusion imaging.

The pathways leading to cerebral infarction include,

1) Necrosis resulting from energy failure and cytoskeletal breakdown
2) Apoptotic pathway- caused by lesser degrees of ischemia

Ischemia starves the neuron of glucose and oxygen and thereby the mitochondrial pathway of ATP formation is affected, leading to dysfunction of the membrane pumps and thereby persistent depolarisation, glutamate release. This increases calcium influx and membrane phospholipid damage releasing free radicals. Free radicals cause oxidant stress and induce apoptosis.

Additional stressors like fever, hyperglycemia and electrolyte disturbances can aggravate the ischemic process and worsens the degree of brain injury and rapid correction of the above is mandatory.

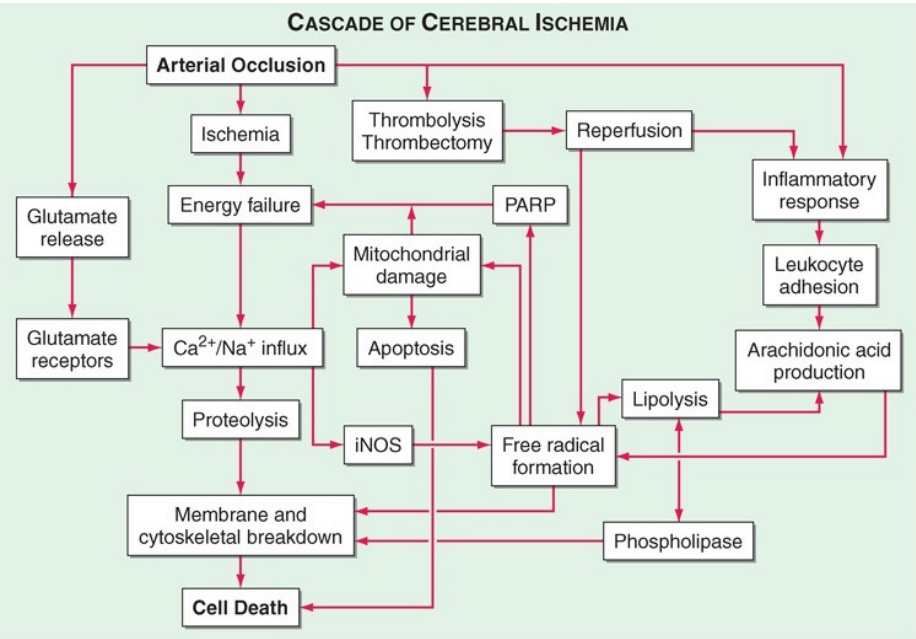


Fig 7. PATHOPHYSIOLOGY OF ISCHEMIC STROKE

HEMORRHAGIC STROKE

10% of strokes are due to Intracerebral haemorrhage. Hypertension, coagulopathy drugs like cocaine and methamphetamine, and cerebral amyloid angiopathy are major causes of ICH. Hypertensive ICH occurs due to spontaneous rupture of penetrating arteries due to high blood pressure. CT imaging is the best investigation for identifying and locating ICH.

Cause	Location	Comments
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid	Coup and contrecoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~100 μm) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Uncommon cause; often associated with prior stroke or underlying vascular anomaly
Drug	Lobar, subarachnoid	Cocaine, amphetamine, phenylpropanolamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–4% per year for bleeding
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; linkage to Alzheimer's disease, rare in patients <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in KRIT1, CCM2, and PDCD10 genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

Fig 8. CAUSES OF INTRACRANIAL HEMORRHAGE

VASCULAR TERRITORIES INVOLVED IN STROKE

The brain parenchyma is supplied by two major arterial territories with a good collaterals through the circle of Willis

The major territories include:

1) Anterior circulation – by the branches of the Internal Carotid Artery- mainly the anterior cerebral, middle cerebral and anterior choroidal arteries
2) Posterior circulation- comprised of Vertebral arteries, basilar artery and posterior cerebral arteries

BLOOD SUPPLY TO BRAIN

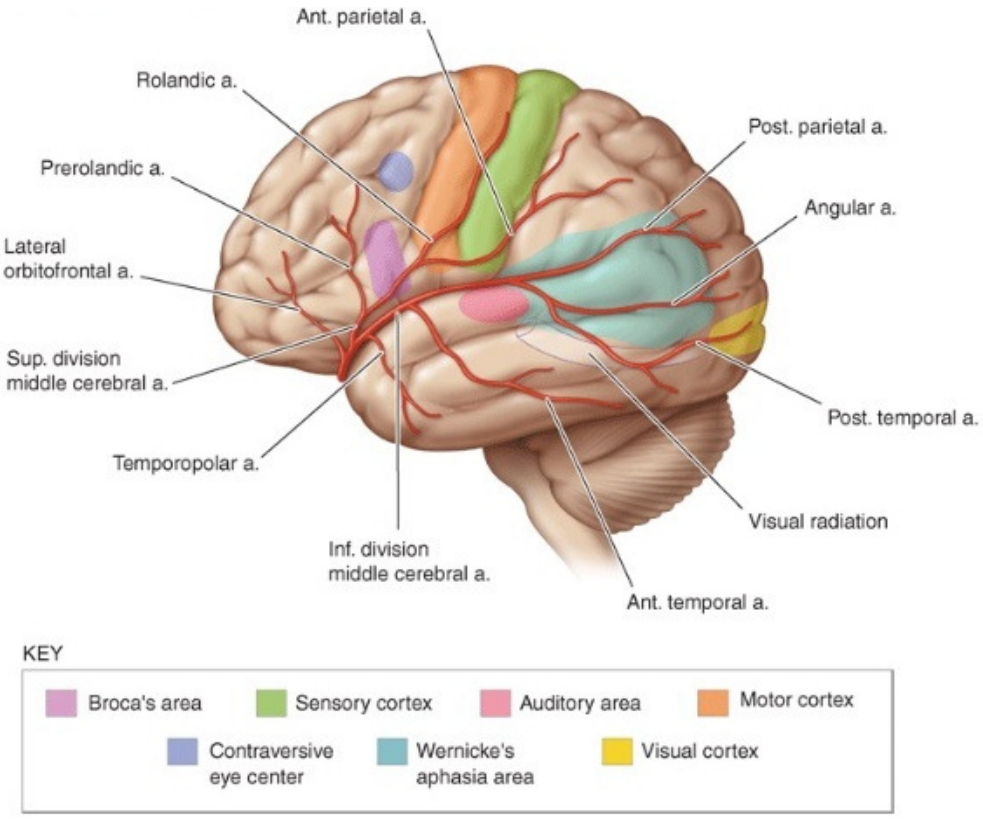


Fig 9.CORTICAL AREAS- LATERAL ASPECT

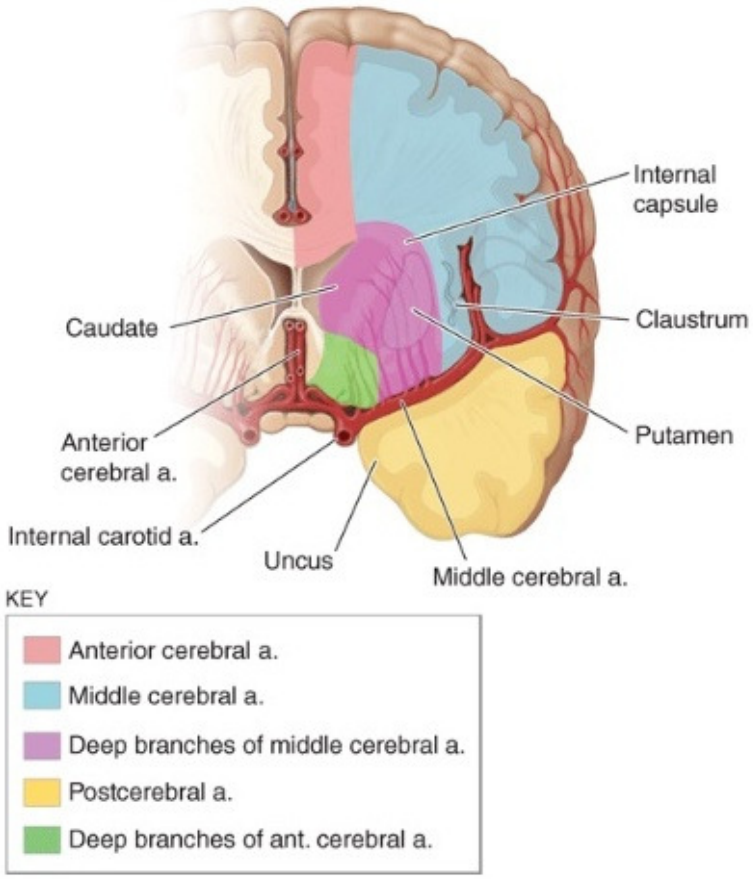


Fig 10. CORTICAL AREAS- CORONAL SECTION

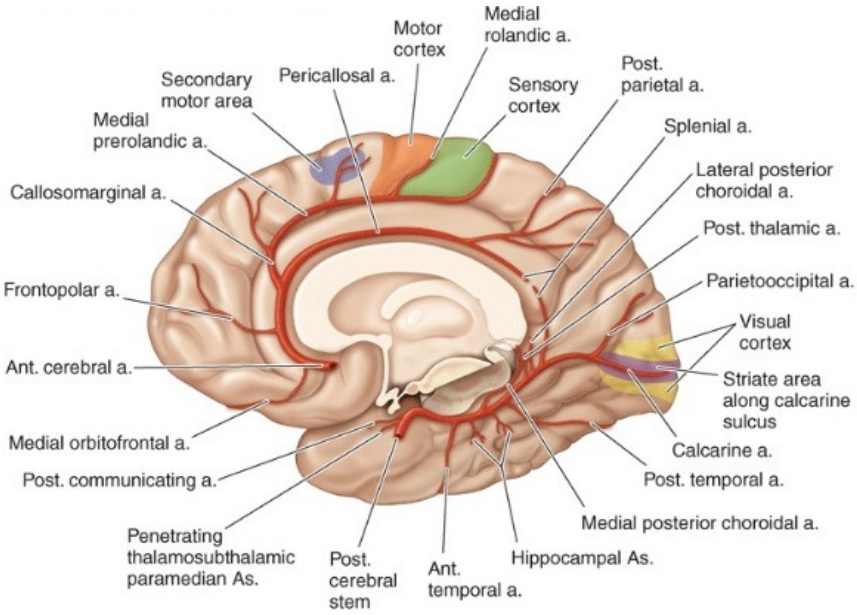


Fig 11. CORTICAL AREAS- MEDIAL ASPECT

Anterior circulation Stroke:

The middle cerebral artery supplies

1) The entire lateral cerebral surface except

a) The frontal pole and a small strip in the superomedial region in frontal and parietal lobes– supplied by the ACA

b) lower temporal and occipital pole convolutions- supplied by the PCA

2) putamen, outer globus pallidus, posterior limb of internal capsule, corona radiata and most of the caudate nucleus – all supplied by the penetrating branches from the proximal MCA

The Anterior cerebral artery is divided into two segments

1) A1 segment gives penetrating branches supplying anterior limb of internal capsule, anterior perforated substance, amygdala, anterior hypothalamus, inferior part of head of caudate nucleus
2) A2 supplies the superomedial surface of the frontal lobe

The Anterior Choroidal Artery –

Arises from the ICA and supplies the posterior limb of the internal capsule and the adjacent posterolateral white mater.

Posterior circulation Stroke

Two patterns of posterior circulation involvement are seen:

1) P1 syndrome- midbrain, subthalamic and thalamic involvement due to occlusion of P1 segment of PCA or its penetrating branches
2) P2 syndrome- Cortical temporal and occipital lobe involvement due to involvement of the PCA distal to the posterior communicating artery (P2 segment)

IMAGING IN STROKE

CT scan

CT serves to exclude or identify hemorrhagic stroke. Generally CTs obtained in the first few hours in ischemic stroke may show no abnormality, for upto 24 to 48 hours.

CT is not the best imaging modality in posterior circulation strokes due to bone artifacts and might miss small cortical surface infarcts.

Contrast enhanced CT can better visualise subacute infarcts, perfusion imaging can detect the ischemic penumbra. CT is sensitive for identifying SAH. CT angiography can identify intracranial aneurysms

Fig 12. CT IMAGING OF INTRACEREBRAL HEMORRHAGE

MRI

MRI can reliably give the extent and the location of the infarct, including a good visualisation of the posterior fossa. Diffusion weighted imaging is very sensitive for acute cerebral infarction. MR perfusion studies with gadolinium contrast can accurately define the penumbra.

Cerebral Angiography

Conventional X-ray cerebral angiography remains the gold standard for quantifying the atherosclerotic stenosis in the cerebral arteries. But this has the risk of arterial damage, embolic stroke and contrast nephropathy and is hence reserved for special situations

Ultrasound

Doppler ultrasound can identify and quantify stenosis at the proximal internal carotid artery. Transcranial Doppler identifies thrombosis in the large intracranial vessels by measuring systolic flow velocity. An MR angiogram

combined with ultrasound techniques can eliminate the need for Conventional cerebral angiography.

Perfusion techniques

Xenon CT and PET can quantify cerebral blood flow but are mainly used in research.

SPECT and MR perfusion techniques can give the relative blood flow.

MR perfusion combined with DW MRI can identify the ischemic penumbra.

TREATMENT OF STROKE

ISCHEMIC STROKE

The immediate goal in acute ischemic stroke is to give adequate perfusion to the ischemic penumbra. Within 6 hours of onset, iv thrombolysis is ideal and the preferred agent is rtPA. Endovascular revascularisation uses intra-arterial thrombolysis. Among the antiplatelets the only drug with proven efficacy is aspirin.

Anticoagulants have not shown significant benefit over risk.

HEMORRHAGIC STROKE

Mortality in acute hypertensive ICH is 40% . the ICH score can stratify the mortality risk of the patients. Any underlying coagulopathy should be rapidly corrected. If patient is on VKA then prothrombin complex concentrates are used. Cerebellar hemorrhages >3cm diameter needs surgical evacuation.

Osmotic agents are administered in case of mass effect or hydrocephalus or coma. Glucocorticoids are not useful in intra-cerebral hematoma induced edema. Prevention of ICH needs blood pressure control in hypertensives, avoidance of excessive alcohol and illicit drugs.

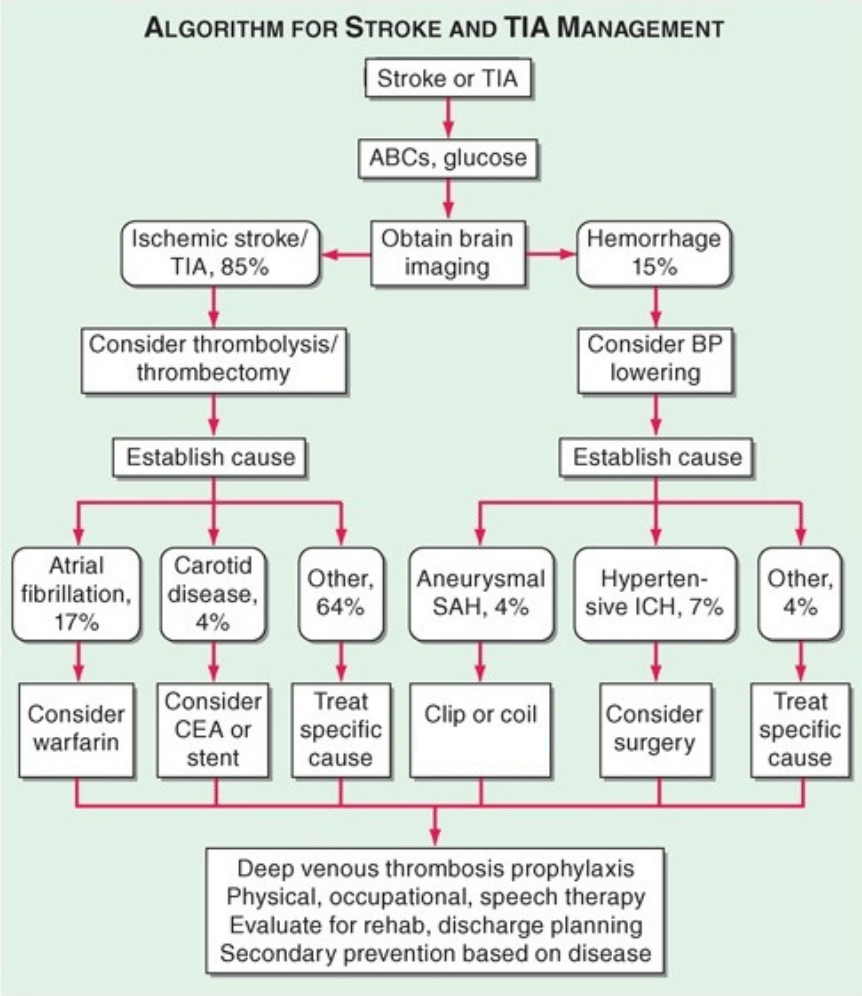


Fig 13. TREATMENT ALGORITHM FOR STROKE

HYPONATREMIA IN STROKE

In patients with stroke, hyponatremia can be a cause of persistent altered sensorium. Neurologic dysfunction in hyponatremia occurs due to cerebral

edema and due to cerebral autoregulation. The complications of hyponatremia are more marked with acute and severe Sodium reductions [40].

If the fall in sodium levels occur within a span of three days, cerebral edema is marked.

The symptoms of nausea and malaise occur at sodium levels 125-130mEq/L. Headache, obtundation, seizures, coma, respiratory failure and non-cardiogenic pulmonary edema can occur at levels 115-120mEq/L. Hyponatremia by resulting in adverse situations like seizures and coma can cause further deterioration of the patient.

Hyponatremia in stroke is mostly hypo-osmolal and is due to either SIADH or CSW [41].

Precipitating factors include dietary sodium restriction, diuretics and infections.

In a study by Sheikh et al, the incidence of hyponatremia in stoke was found to be 35% out of which 67% had SIADH and 33% had CSW. Hyponatremia had significant impact on the outcome especially in patients with CSW [40].

In another study by Huang WY et al, hyponatremia in acute stroke was seen in 11.6%. Hyponatremia was also a predictor of three-year mortality in acute ischemic stroke patients [41].

MATERIALS & METHODS

MATERIALS AND METHODS

(i) SOURCE OF DATA **:** Data consists of primary data collected by the principal investigator directly from the patients who are admitted in the Government Medical College and Hospital

(ii) STUDY AREA: Coimbatore Medical College hospital

(iii) DESIGN OF STUDY: Cross sectional study

(iv) PERIOD OF STUDY: One year, July 2014- July 2015

(v) SAMPLE SIZE: Based on past records and previous evidence, it is expected that about fifty number of cases would be available during the period of study.

(vi) DEFINITION USED IN THE STUDY

- **STROKE**

  "Neurological deficit of cerebrovascular cause that persists beyond 24 hours"

- **HYPONATREMIA**

  Hyponatremia is defined as sodium level < 130 meq/L

  True hyponatremia is defined as those patients with a sodium level of 130 meq/L and plasma osmolality less 275 mosm/kg

- **PLASMA OSMOLALITY**

  The plasma osmolality is calculated using the formula-

  2(Na)+ Glu/18+ BUN/2.8

  (Na- Plasma Sodium, Glu-Plasma glucose, BUN- Blood urea nitrogen)

- **SODIUM CORRECTION**

Total body water (TBW) - 50% of body weight in females

60% of body weight in males

Free water deficit-[(Na^+ - 140) / 140]* TBW

Free water clearance- V * [1- (U_{Na} +$U_{K)}$ / P_{Na}]

V- Urinary volume; U_{Na} - Urinary sodium, U_K - Urinary potassium;

P_{Na}- Plasma Sodium

NORMAL RANGES OF PARAMETERS USED IN THE STUDY

Plasma Osmolality	-	275 – 295 mosm/kg
Serum Potassium	-	3.5- 5 m Eq/L
Serum Albumin	-	3.5- 5 g/dl
Hematocrit	-	Male: 40.7-50%
		Female: 36.1-44.3%
Serum Uric acid	-	Male: 3.4-7 mg/dl
		Female: 2.4-6 mg/dl
BUN/ Creatinine	-	10:1-20:1

INCLUSION CRITERIA:

Confirmed cases of stroke by history, neurologic and imaging modalities.

EXCLUSION CRITERIA:

The following patients are excluded:

- Head injury

- CNS tumor
- Pulmonary tuberculosis
- Bacterial pneumonia
- Bronchogenic carcinoma
- Hematologic malignancies
- Recent surgery
- Meningitis
- Encephalitis
- Drug usage- SSRI, TCA, narcotics, NSAIDs, Antipsychotics, Carbamazepine, Cyclophosphamide, clofibrate, chlorpropamide

About 50 stroke patients admitted to Coimbatore Medical College Hospital during the one year study period (August 2014 to September 2015) were studied.

The diagnosis was confirmed by imaging- CT scan or MRI.

The stroke type- ischemic or hemorrhagic, the side of the stroke and the involved vascular territory was confirmed using the imaging study.

After ruling out the exclusion criteria, serial serum sodium levels were done. In patients with hyponatremia, plasma osmolality was measured to differentiate between true and pseudo-hyponatremia. Cerebral causes of hyponatremia were identified and classified as SIADH/CSW and treated as per the standard protocol. The patient was put on in-patient follow-up till

discharge/ death. The patients with prior/ admission diuretic usage are not taken into the study group as cases.

Day1

Clinical estimation of Extracellular fluid volume – estimated by

Jugular venous pressure elevation,

Peripheral edema,

Negative/ positive fluid balance by input /output,

Blood pressure levels

On Day 1 of hyponatremia, levels of

Serum Sodium

Plasma osmolality

Serum potassium

Serum uric acid

Hematocrit

BUN/ Creatinine ratio

Serum albumin

Urine Sodium are measured.

This helps in tentative differentiation between SIADH and CSW.

Based on Day 1 values,

Sodium correction is carried out using the standard protocols i.e., fluid restriction in case of SIADH and intravenous saline in case of suspected CSW; hypertonic saline where severe hyponatremia is encountered.

Serial Day 5 values

Serum sodium,

Serum uric acid,

Hematocrit,

Serum albumin

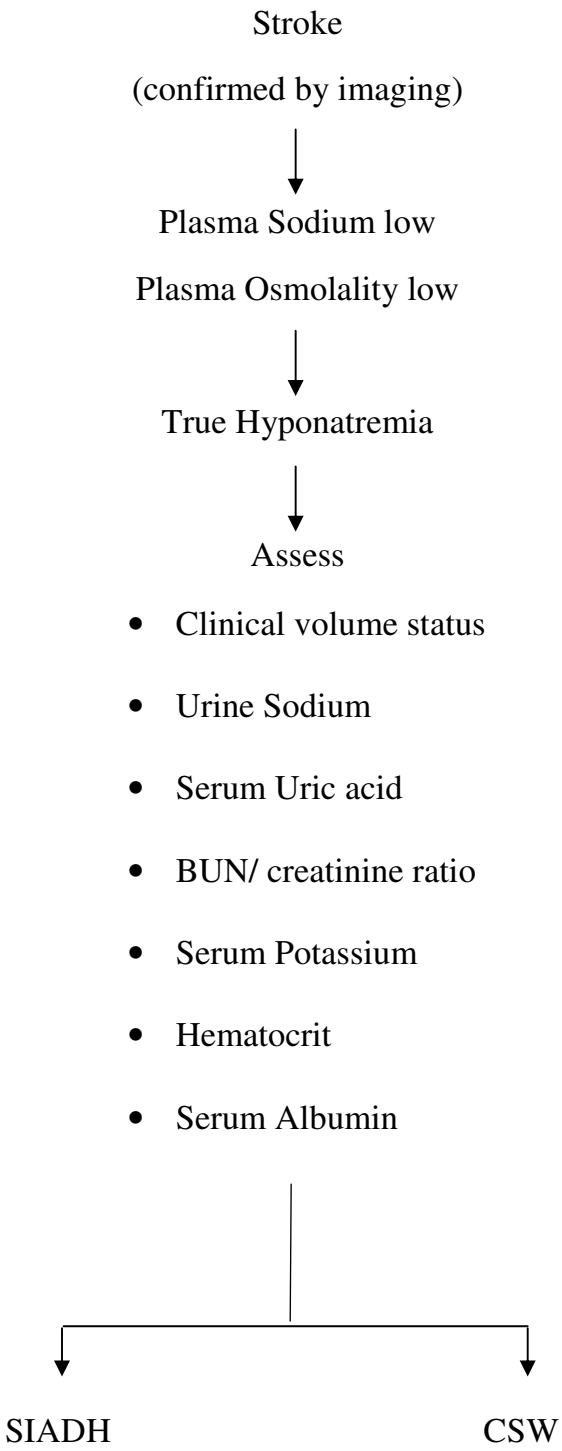
were measured and confirmatory assessment of SIADH / CSW was made.

A short term follow up of the outcome of the patient till discharge/ death was done to see whether hyponatremia could affect the outcome of the patient significantly.

INVESTIGATIONS

- Chest X-ray
- CT scan brain/ MRI brain
- Plasma osmolality
- Urine sodium
- Plasma sodium
- Serum Potassium
- Hematocrit
- Serum Uric acid
- Serum Albumin
- BUN / Creatinine ratio

DIAGNOSTIC APPROACH



STATISTICAL ANALYSIS

The data are reported as the mean +/- SD or the median, depending on their distribution.

The differences in quantitative variables between groups were assessed by the unpaired t test.

Comparison between groups was made by the Non parameteric Mann - whitney test

ANOVA was used to assess the quantative variables.

A Chi Square test was used to assess differences in categoric variables between groups.

Kaplan Meiyer was performed

A p value of <0.05 using a two-tailed test was taken as being of significance for all statistical tests.

All data were analysed with the statistical software package. (SPSS, version 16.0 for windows)

RESULTS

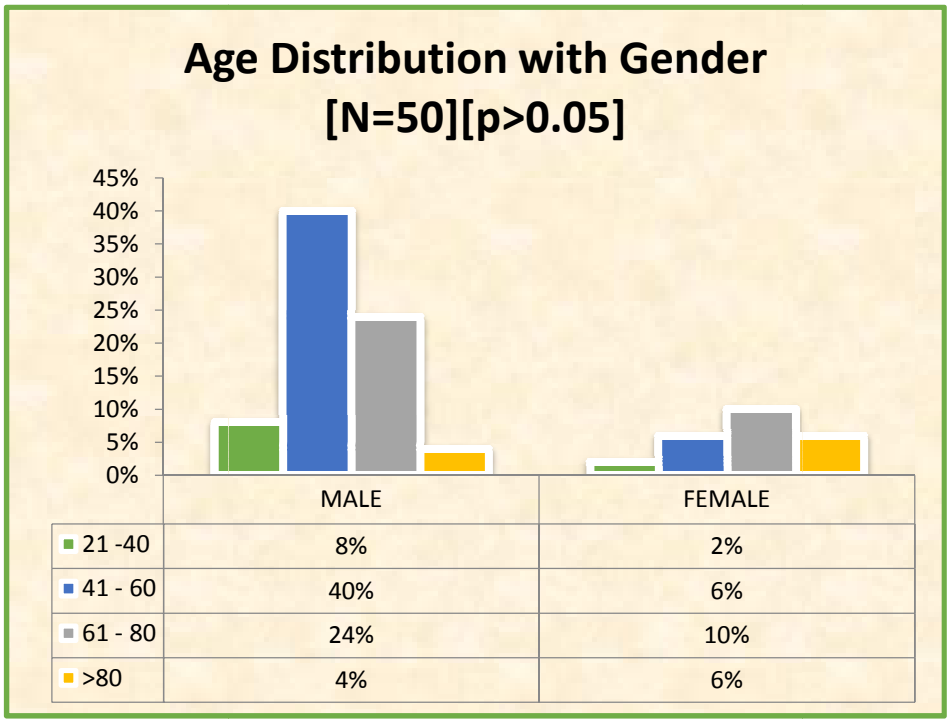
RESULTS

STROKE ANALYSIS

TABLE 1. AGE DISTRIBUTION

	GENDER			
AGE	MALE	FEMALE	TOTAL	(%)
21 -40	4	1	5	10%
41 – 60	20	3	23	46%
61 – 80	12	5	17	34%
>80	2	3	5	10%
TOTAL	38	12	50	

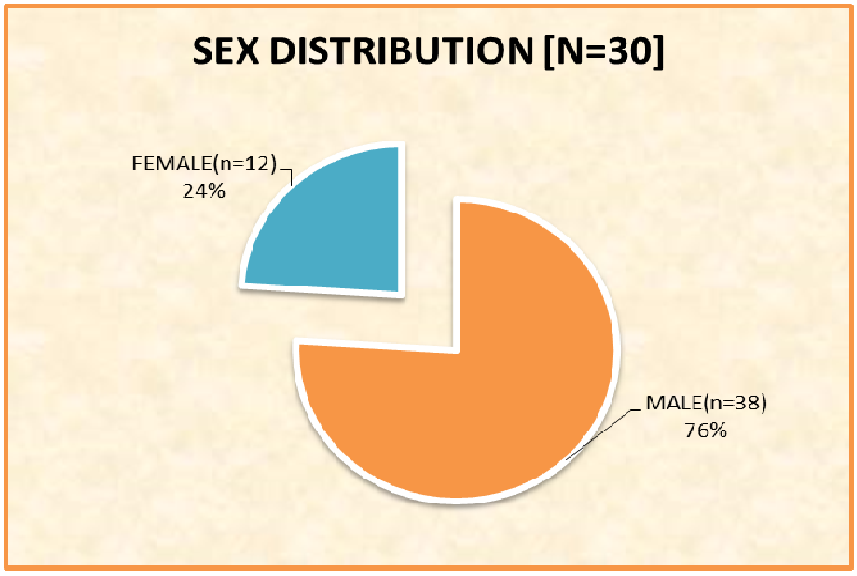
CHART 1. COMPARISION OF AGE DISTRIBUTION WITH GENDER



In our set of stroke patients, the majority of the patients, around 46% (n= 23) belonged to the middle aged group (40 – 60 years of age), 10% of patients belonged to the extreme age groups, <40 years and >80 years.

The majority of males belonged to 40-60 years age group, (n=20). The prevalence of stroke in females was most seen to be in the 60 to 80 year age group (n=5)

CHART 2. SEX DISTRIBUTION

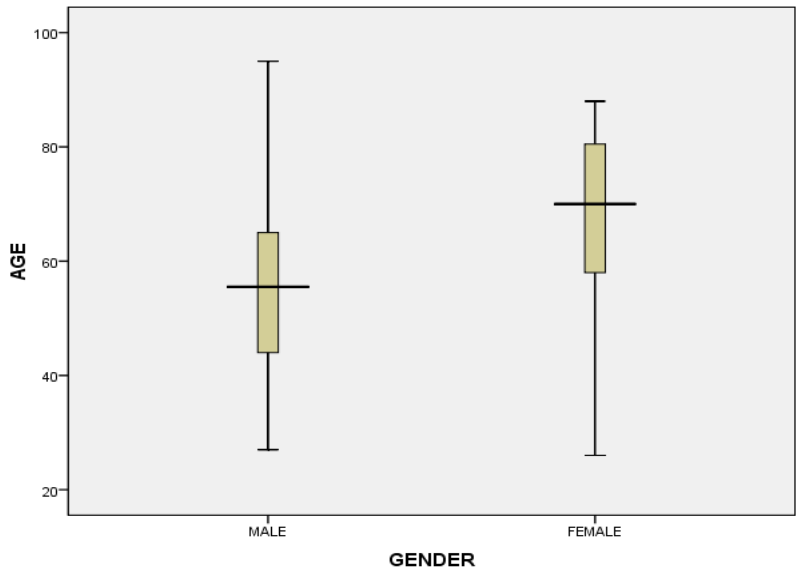


Of the 50 stroke patients 76% (n= 38) are male and 24% (n= 12) were female

TABLE 2. MEAN AGE WITH GENDER COMPARISION

Mean Age with Gender							
	Mean		95% CI for Mean				
Gender	[Years]	SD	Lower	Upper	Minimum	Maximum	Sig
MALE	56.2	14.5	51.4	61.0	27	95	
FEMALE	66.9	17.3	55.9	77.9	26	88	<0.05
Total	58.8	15.8	54.3	63.2	26	95	

CHART 3. BOX PLOT OF AGE vs GENDER



In our study group patients, we found

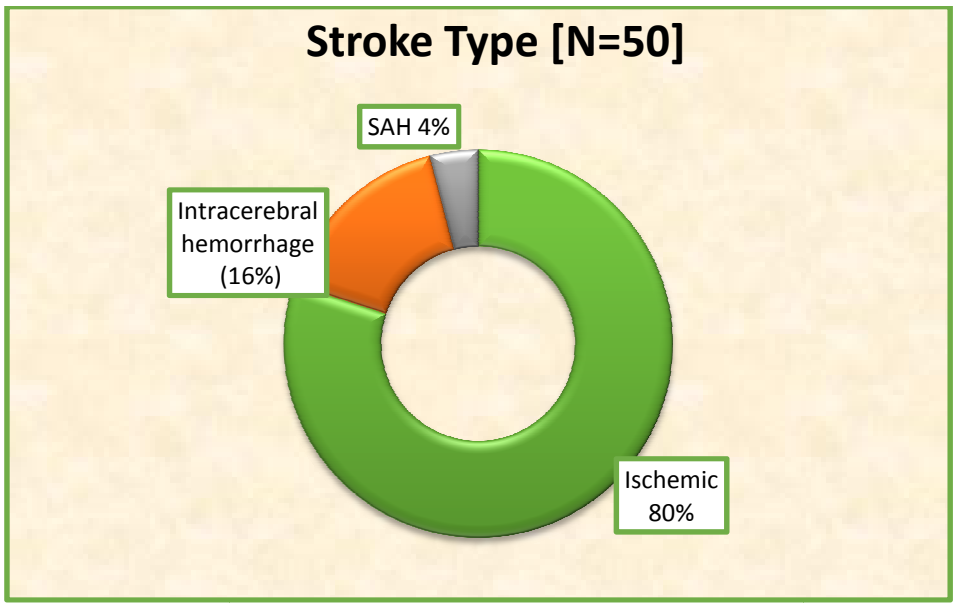
The mean age of males with stroke to be 56.2 (± 14.5)

The mean age of the females with stroke to be 66.9 (± 17.3)

TABLE 3. STROKE TYPE

STROKE TYPE	n	(%)
Ischemic	40	80%
Intracerebral Hemorrhage	8	16%
Subarachnoid Hemorrhage	2	4%
Total	50	100%

CHART 4. STROKE TYPE

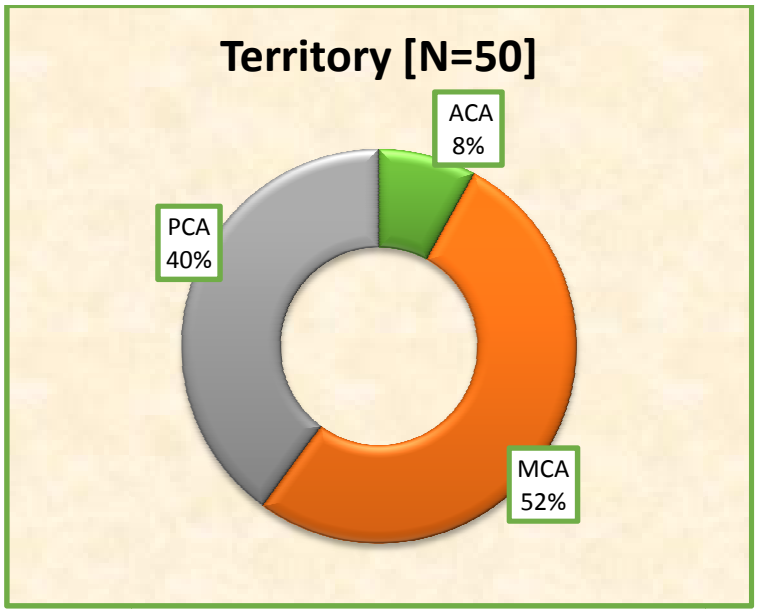


In our study, the majority of the patients had ischemic stroke around 80% (n=40), of which 6 patients had lacunar stroke, 5 patients had a massive infarct. Hemorrhagic stroke was seen in 10 patients, with 8 patients (16%) having intracerebral bleed. In 4 patients with intra cerebral bleed, the cause of haemorrhage was accelerated hypertension. 2 patients with hemorrhagic stroke had aneurysmal bleed presenting sub-arachnoid haemorrhage (4%)

TABLE 4. STROKE TERRITORY

TERRITORY	n	(%)
ACA	4	8%
MCA	26	52%
PCA	20	40%
Total	50	100%

CHART 5. STROKE TERRITORY

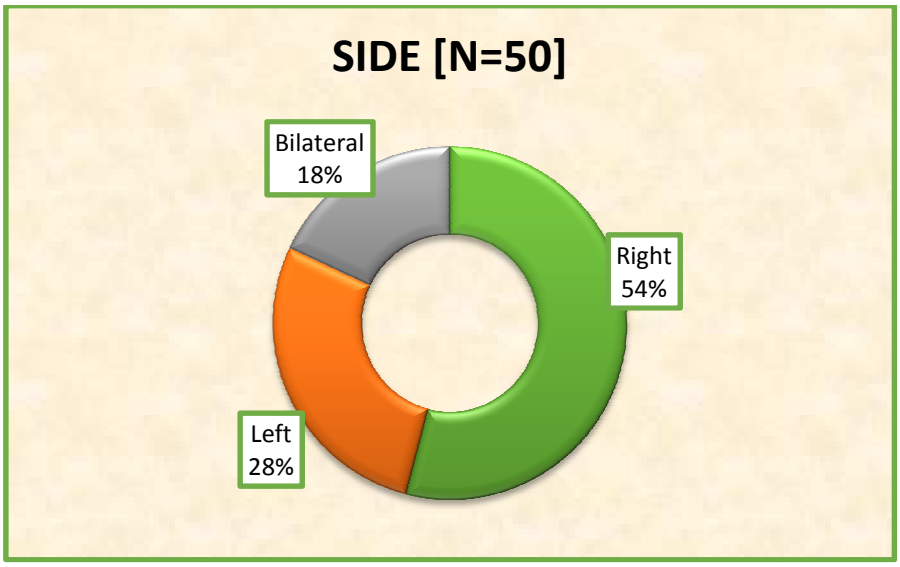


The majority of patients in our study i.e., 26 patients (52%), had stroke corresponding to the Middle Cerebral Artery territory, followed by 20 patients (40%) with Posterior cerebral artery involvement and 4 patients (8%) with Anterior Cerebral circulation involvement.

TABLE 5. SIDE OF THE CEREBRAL INVOLVEMENT

SIDE	N	(%)
Right	27	54%
Left	14	28%
Bilateral	9	18%
Total	50	100%

CHART 6. SIDE OF CEREBRAL INVOLVEMENT



In our study, most of the patients had Right sided stroke 54% (n=27), 28% had left sided stroke (n=14) and 18% (n=9) had bilateral involvement.

TABLE 6: ASSOCIATION OF DEMOGRAPHIC VARIABLES & CLINICAL VARIABLES WITH HYPONATREMIA

Clinical Variables	HYPONATREMIA				
	Without [n=37]	**SIADH [n=6]**	**CSW [n=4]**	**Others[n=3]**	**Sig**
AGE					
21 -40	5	0	0	0	
%	14%	0%	0%	0%	
41 – 60	21	2	0	0	
%	57%	33%	0%	0%	<0.05
61 – 80	7	4	3	3	
%	19%	67%	75%	100%	
>80	4	0	1	0	
%	11%	0%	25%	0%	
GENDER					
Male	30	4	3	1	
%	81%	67%	75%	33%	
Female	7	2	1	2	
%	19%	33%	25%	67%	>0.05
Types of Stroke					
Ischemic	30	5	2	3	
%	81.10%	83.30%	50.00%	100.00 %	
Hemorrhagic	7	1	0	0	
%	18.90%	16.70%	0.00%	0.00%	<0.001
Ischemic+Hemorrhagic	0	0	2	0	
%	0.00%	0.00%	50.00%	0.00%	
TERRITORY					
ACA	4	0	0	0	
%	10.80%	0.00%	0.00%	0.00%	
MCA	20	2	3	3	
%	54.10%	33.30%	75.00%	100.00 %	>0.05
PCA	13	4	1	0	
%	35.10%	66.70%	25.00%	0.00%	
SIDE					
RIGHT	20	4	3	0	
%	54.10%	66.70%	75.00%	0.00%	
LEFT	12	1	0	1	
%	32.40%	16.70%	0.00%	33.30%	>0.05
BILATERAL	5	1	1	2	
%	13.50%	16.70%	25.00%	66.70%	

TABLE 7.ASSOCIATION OF BIO CHEMICAL PROPERTIES WITH HYPONATREMIA

BIO CHEMICAL PROPERTIES				
Clininal Variables	HYPONATREMIA			
	SIADH [n=6]	CSW [n=4]	Others[n=3]	Sig
Volume Status				
Increased	3	0	0	
%	50.00%	0.00%	0.00%	
Decreased	0	4	0	
%	0.00%	100.00%	0.00%	<0.05
Normal	3	0	0	
%	50.00%	0.00%	0.00%	
Uric Acid -day5				
Decreased	0	3	0	
%	0.00%	75.00%	0.00%	<0.05
Normal	5	0	0	
%	100.00%	0.00%	0.00%	
1BUN/ Creatinine				
Increased	0	4	1	
%	0.00%	100.00%	33.30%	
Decreased	5	0	0	
%	100.00%	0.00%	0.00%	<0.05
Normal	0	0	1	
%	0.00%	0.00%	33.30%	
HCT Day5				
Increased	0	2	0	
%	0.00%	50.00%	0.00%	
Decreased	2	0	0	
%	33.30%	0.00%	0.00%	<0.05
Normal	4	1	0	
%	66.70%	25.00%	0.00%	
Albumin Day 5				
Decreased	1	0	0	
%	16.70%	0.00%	0.00%	<0.05
Normal	5	3	0	
%	83.30%	75.00%	0.00%	
Urine Sodium				
Increased	6	4	1	
%	100.00%	100.00%	33.33%	
Decreased	0	0	2	
%	0.00%	0.00%	66.67%	<0.05

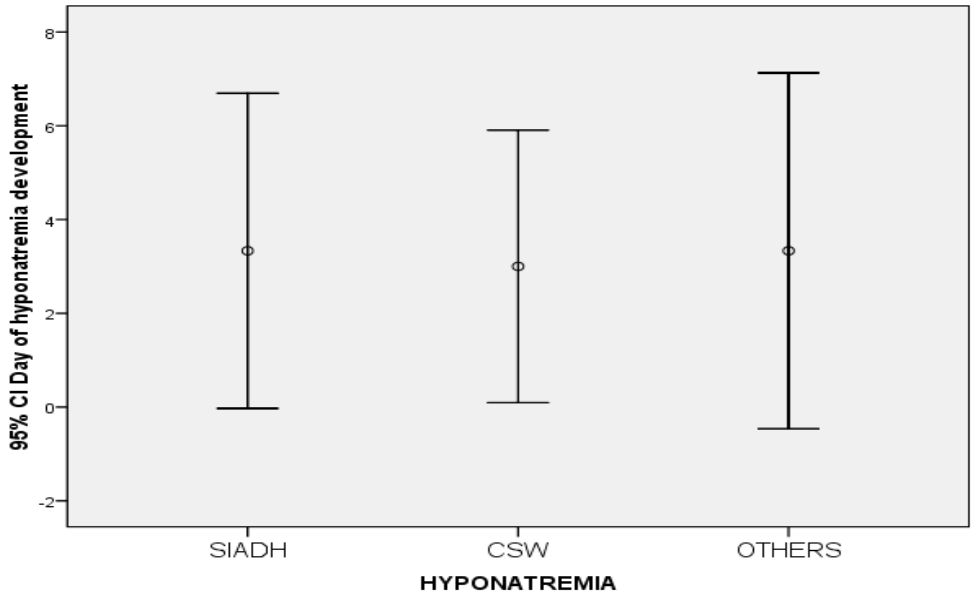
TABLE. 8 CLINICAL VARIABLES MEAN

	Hyponatremia	Mean	SD	95% CI for Mean		Minimum	Maximum	Maximum
				Lower	Upper			
Na Day 1	With	127.08	3.252	125.11	129.04	117	130	
	without	139.03	4.2	137.63	140.43	130	148	<0.001
	Total	135.92	6.602	134.04	137.8	117	148	
Plasma Osmo	With	270.52	16.17	260.75	280.30	248	299	

TABLE 9. MEAN DAY OF HYPONATREMIA DEVELOPMENT

Hyponatremia	Mean [Days]	SD	95% CI for Mean		Minimum	Maximum	Sig
			Lower	Upper			
SIADH	3.3	3.2	0.0	6.7	1	9	
CSW	3.0	1.8	0.1	5.9	1	5	
Others	3.3	1.5	-0.5	7.1	2	5	>0.05
Total	3.2	2.4	1.8	4.7	1	9	

CHART 7. MEAN DAY OF HYPONATREMIA DEVELOPMENT

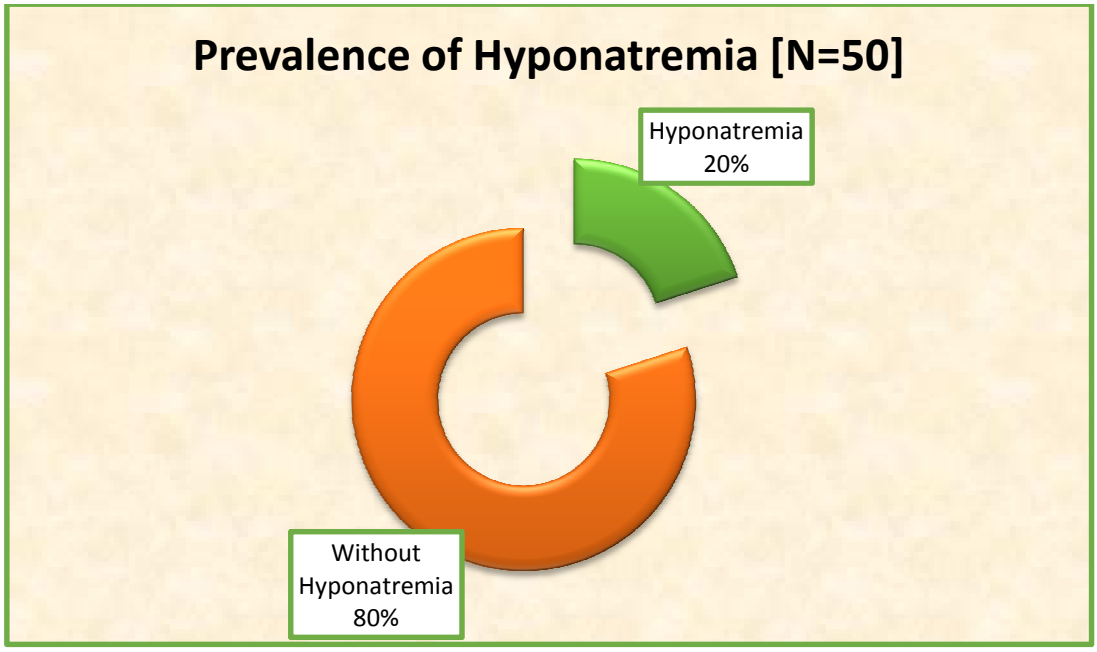


The mean day of development of hyponatremia was 3.2 days and there was no significant difference in the day of development of hyponatremia between the various groups. ($p>0.05$)

TABLE 10. PREVALENCE OF HYPONATREMIA

	n	(%)
Hyponatremia	10	20%
Without Hyponatremia	40	80%
Total	50	100%

CHART 8. PREVALENCE OF HYPOATREMIA



The prevalence of hyponatremia due to cerebral causes was noted in 20% of the 50 studied stroke patients (n=10)

TABLE 11. PREVALENCE OF SIADH AND CSW

	n	(%)
SIADH	6	12%
CSW	4	8%
Others	3	6%
Total	13	26%

CHART 9. PREVALENCE OF SIADH AND CSW

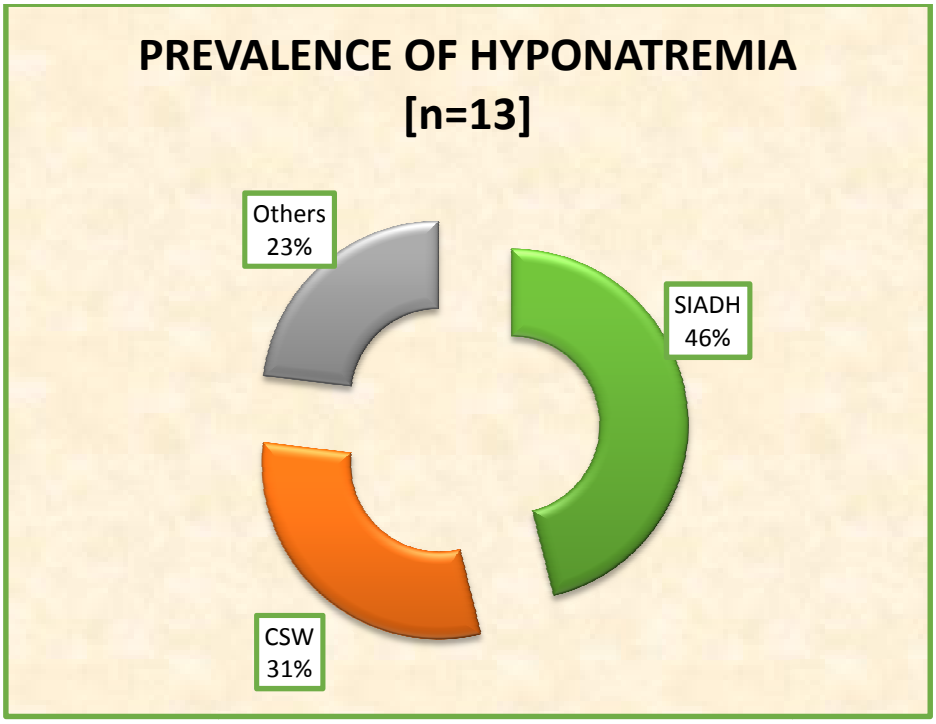
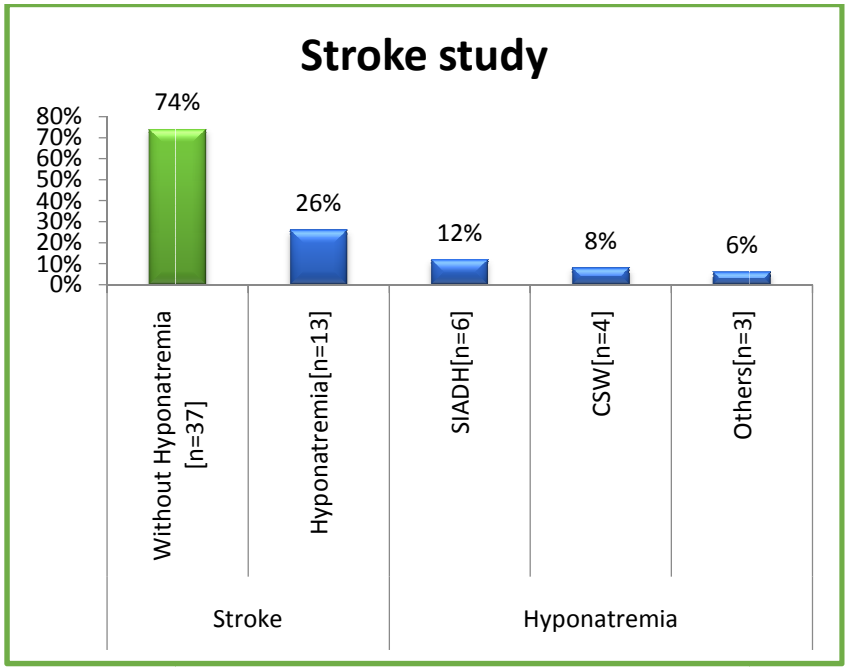


CHART 10. HYPONATREMIA PREVALENCE IN STROKE

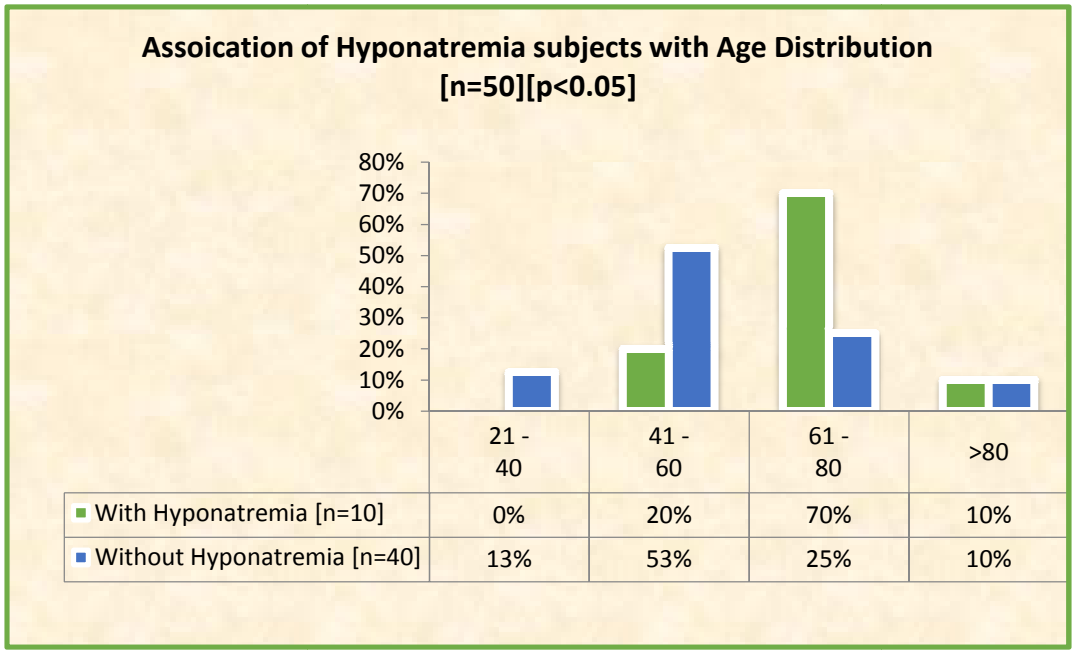


Of the 50 patients, 12% had SIADH (n=6) and 8% had CSW (n=4),Other causes of hyponatremia were found in 6% (n=3) which were attributed to diarrhoea (n=1), renal failure (n=1) and congestive cardiac failure (n=1).

TABLE 12. AGE DISTRIBUTION IN STROKE

	HYPONATREMIA			
AGE	WITH	WITHOUT	TOTAL	(%)
21 -40	0	5	5	10%
41 - 60	2	21	23	46%
61 - 80	7	10	17	34%
>80	1	4	5	10%
TOTAL	10	40	50	

CHART 11. AGE DISTRIBUTION IN STROKE

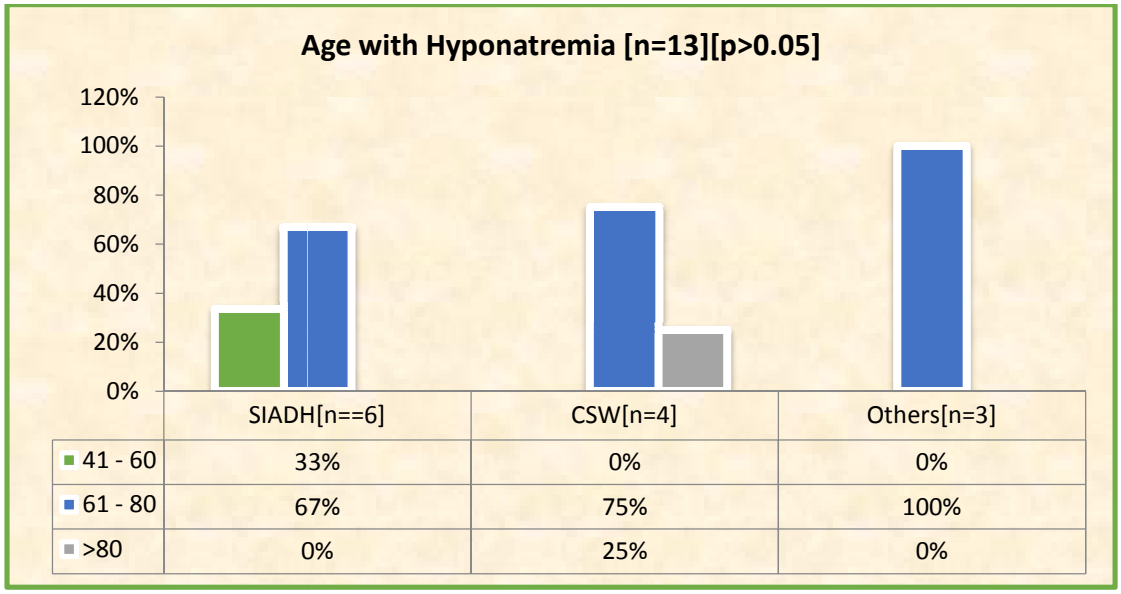


In general, the occurrence of hyponatremia due to cerebral causes was noted most in the 61-80 year age group i.e., 70% (n=10). The occurrence of hyponatremia was 20% in 41-60 year age group and 10% in the > 80 year age group.The difference in the hyponatremia prevalence among the various age groups reached statistical significance ($p<0.05$)

TABLE 13. AGE DISTRIBUTION OF SIADH AND CSW

	Hyponatremia				
Age	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
41 - 60	2	0	0	2	15%
61 - 80	4	3	3	10	77%
>80	0	1	0	1	23%
Total	6	4	3	13	

CHART 12. AGE DISTRIBUTION OF SIADH AND CSW

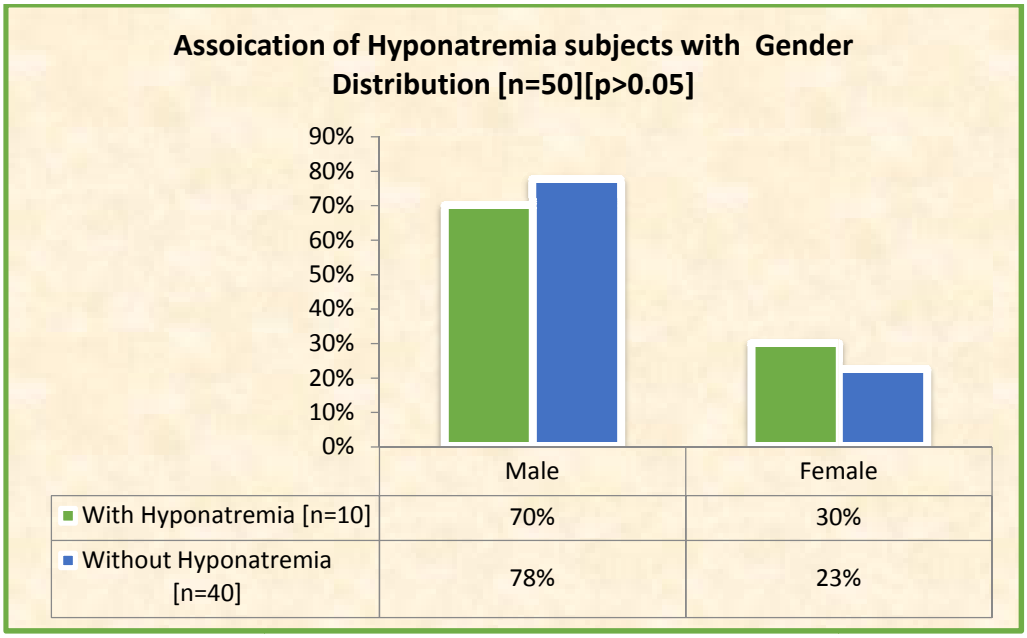


All the patients who developed SIADH were of the age group of 41-80 years, with about 67% (n=4) coming under the 61-80 year age group. The occurrence of SIADH was 33% in the 41-60 year age group. All the patients who developed Cerebral Salt Wasting on the other hand belonged to the age group of 61 years and above, with the majority belonging to the 61-80 year age group, 75% (n=3). The occurrence of CSW in the age group >80 years was 25%

TABLE 14. GENDER DISTRIBUTION IN HYPONATREMIA

	HYPONATREMIA			
Gender	WITH	WITHOUT	TOTAL	(%)
Male	7	31	38	76%
Female	3	9	12	24%
TOTAL	10	40	50	

CHART 13. GENDER DISTRIBUTION IN HYPONATREMIA

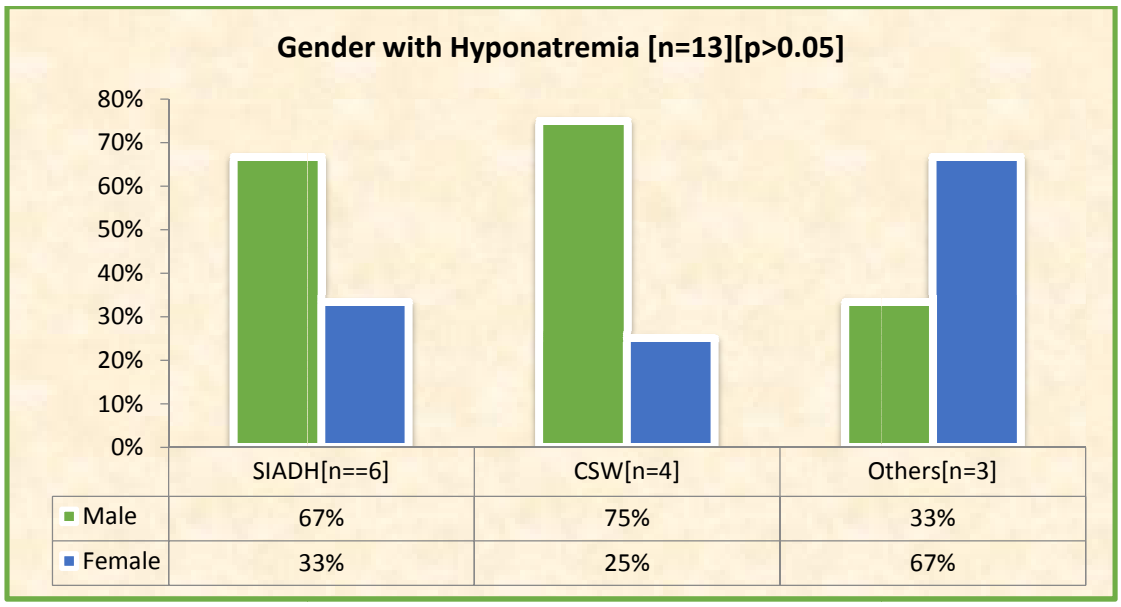


Of the patients with hyponatremia due to cerebral cause, 70% (n=7) were males and 30% (n=3) were females. There was no significant difference in the incidence of hyponatremia based on the gender (p>0.05)

TABLE 15. GENDER DISTRIBUTION OF SIADH AND CSW

	Hyponatremia				
Gender	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
Male	4	3	1	8	62%
Female	2	1	2	5	23%
Total	6	4	3	13	

CHART 14. GENDER DISTRIBUTION OF SIADH AND CSW

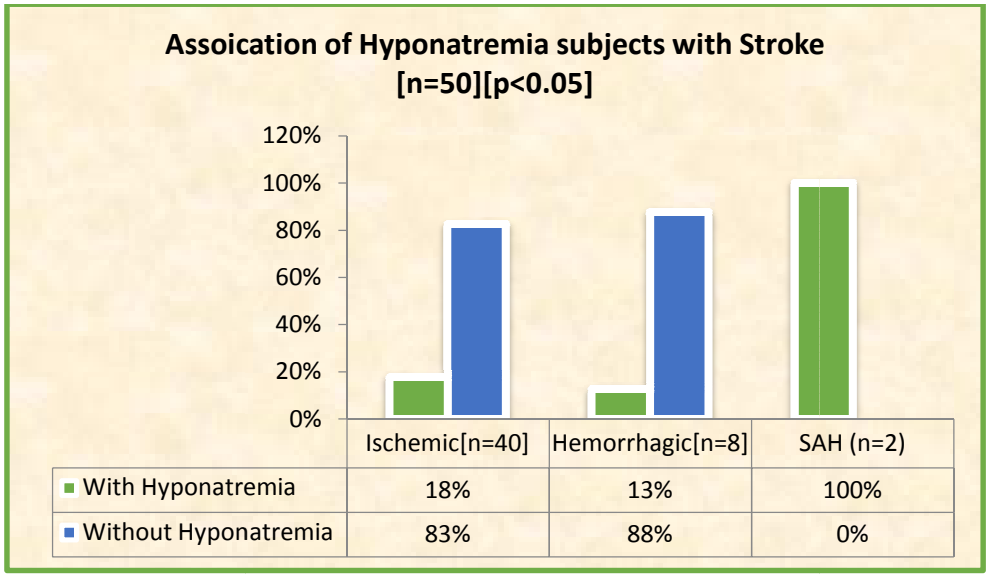


In the SIADH group, the majority of patients were males 67% (n=4) and females comprised of 33% (n=2). In the CSW group also the gender of majority of the patients was male 75% (n=3), whereas females comprised about 25% (n=1). The variation in sex distribution among the various groups did not reach statistical significance.($p > 0.05$). In the group of patients who had other causes of hyponatremia, the majority were females, 67%.

TABLE 16. STROKE TYPE IN HYPONATREMIA

	HYPONATREMIA			
STROKE TYPE	WITH	WITHOUT	TOTAL	(%)
Ischemic	7	33	40	80%
Intracerebral hemorrhage	1	7	8	16%
SAH	2	0	2	4%
TOTAL	10	40	50	

CHART 15. STROKE TYPE IN HYPONATREMIA

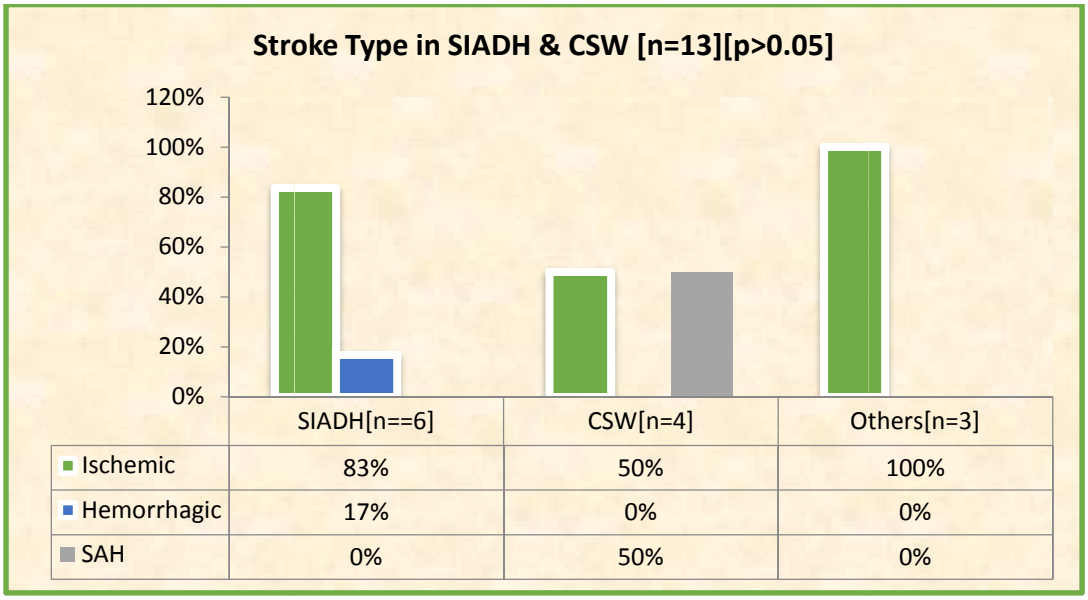


All the subarachnoid haemorrhage patients in our study developed hyponatremia(n=2).Out of the Ischemic stroke patients 18% had hyponatremia. (n=7). Hyponatremia was seen in 13% of patients with intracerebral haemorrhage.

TABLE 17. STROKE TYPE IN SIADH AND CSW

	Hyponatremia				
Stroke Type	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
Ischemic	5	2	3	10	77%
Hemorrhagic	1	0	0	1	8%
SAH	0	2	0	2	23%
Total	6	4	3	13	

CHART 16. STROKE TYPE IN SIADH AND CSW

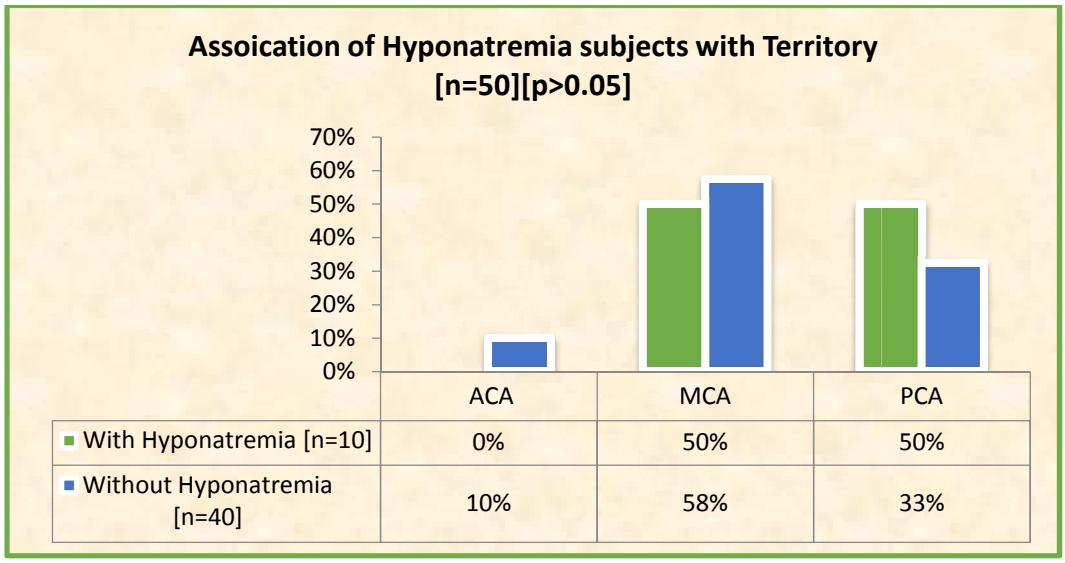


Among patients with hyponatremia, 77% had ischemic stroke (n=10), 8% had intra-cerebral haemorrhage (n=1), and 23% (n=2) had sub-arachnoid haemorrhage. Among SIADH patients, 73% had ischemic stroke and 18% had intra cerebral hemorrhage. Among cerebral salt wasting patients, ischemic stroke was found in 50% of patients and SAH was found in 50% patients. The difference in stroke type seen in the various conditions did not however, reach statistical significance.

TABLE 18. STROKE TERRITORY IN HYPONATREMIA

	HYPONATREMIA			
TERRITORY	WITH	WITHOUT	TOTAL	(%)
ACA	0	4	4	8%
MCA	5	23	28	56%
PCA	5	13	18	36%
TOTAL	10	40	50	

CHART 17. STROKE TERRITORY IN HYPONATREMIA

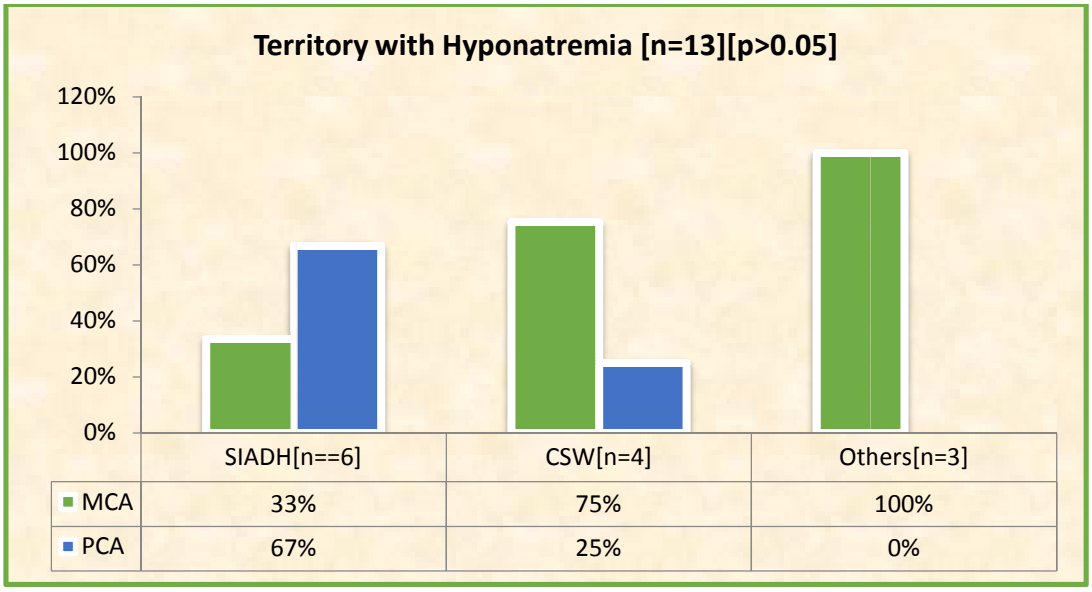


50% of the hyponatremia patients had Posterior Cerebral Artery territory involvement and 50% had Middle cerebral Artery territory involvement. None of our patients with ACA territory stroke developed hyponatremia.

TABLE 19. TERRITORY IN SIADH AND CSW

	Hyponatremia				
Territory	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
MCA	2	3	3	8	62%
PCA	4	1	0	5	23%
Total	6	4	3	13	

CHART 18. TERRITORY IN SIADH AND CSW



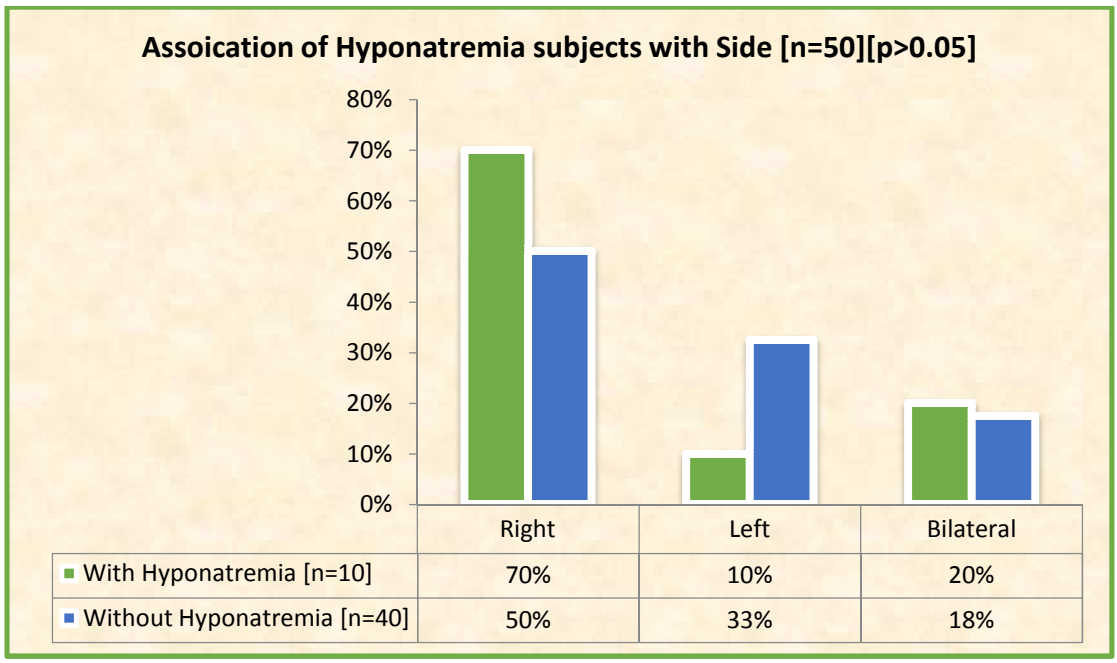
The majority of patients with SIADH had a posterior circulation stroke, 67% (n= 4), and 33% (n=2 had Middle Cerebral Territory stroke.

In CSW, 75% (n=3) had Middle Cerebral Artery territory involvement and 25% had posterior circulation stroke. In the group with other causes of hyponatremia, the territory involved was the Middle cerebral artery territory

TABLE 20. SIDE OF CEREBRAL INVOLVEMENT IN HYPONATREMIA

	HYPONATREMIA			
SIDE	WITH	WITHOUT	TOTAL	(%)
Right	7	20	27	54%
Left	1	13	14	28%
Bilateral	2	7	9	18%
TOTAL	10	40	50	

CHART 19. SIDE OF CEREBRAL INVOLVEMENT



Of the patients with cerebral cause of hyponatremia, 70% had a right sided involvement, 20% had bilateral and 10% had left sided involvement.

TABLE 21. SIDE vs SIADH AND CSW

	Hyponatremia				
SIDE	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
Right	4	3	0	7	54%
Left	1	0	1	2	15%
Bilateral	1	1	2	4	23%
Total	6	4	3	13	

4 patients with SIADH and 3 patients with CSW had right sided involvement. Left sided involvement was seen in 1 patient with SIADH. 2 patients (1- SIADH and 1- CSW) had bilateral arterial involvement.

TABLE 22. DURATION OF HOSPITAL STAY

Hyponatremia	Mean [Days]	SD	95% CI for Mean		Minimum	Maximum	Sig
			Lower	Upper			
WITH	17	34.247	-3.7	37.7	1	130	
WITHOUT	3.73	1.866	3.11	4.35	1	10	<0.05
Total	7.18	18.01	2.06	12.3	1	130	

The mean duration of hospital stay was significantly different in patients with hyponatremia 17 days as against 3.73 days in normonatremic patients

The maximum duration of stay seen in one of the hyponatremic patients was 130 days.

CHART 20. DURATION OF HOSPITAL STAY

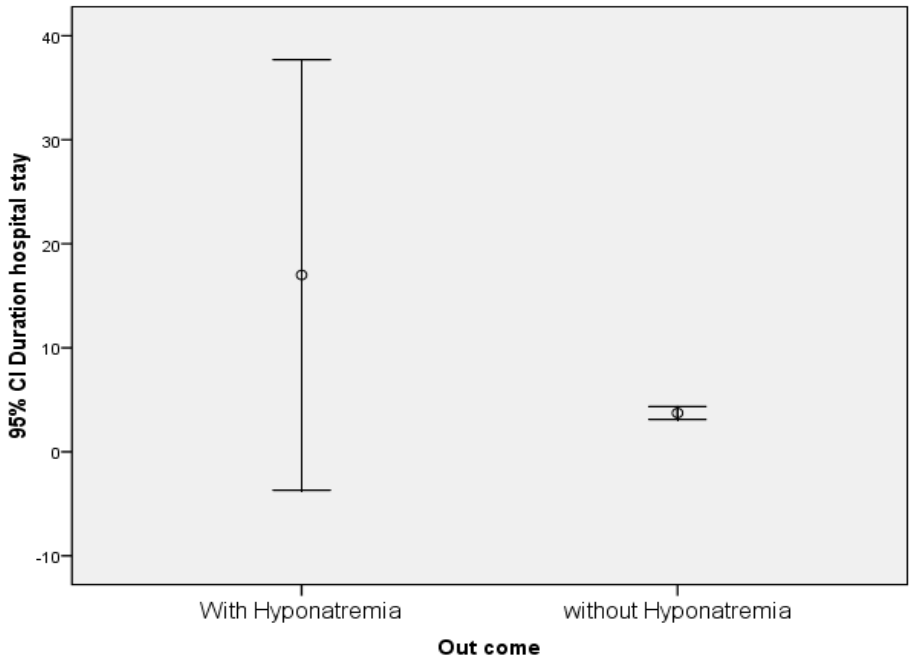


TABLE 23. SURVIVAL TIME

Kaplan-Meier							
Means and Medians for Survival Time							
Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
92.411	13.566	65.823	119	130	0	.	.

a. Estimation is limited to the largest survival time if it is censored.

CHART 21. SURVIVAL TIME

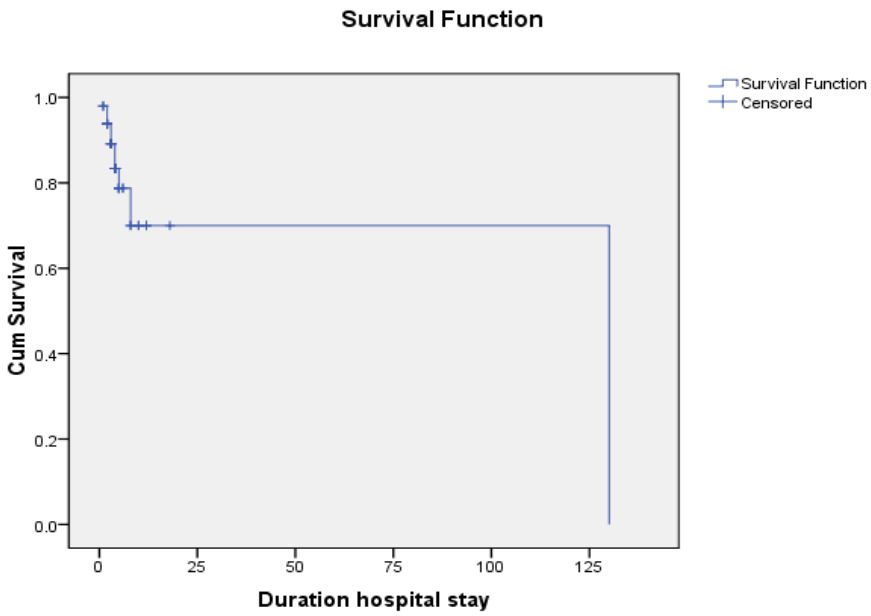


TABLE 24. SURVIVAL TIME vs AGE

Means and Medians for Survival Time vs Age

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
80.899	3.106	74.812	86.986	81	4.865	71.464	90.536

a. Estimation is limited to the largest survival time if it is censored.

CHART 22. SURVIVAL TIME vs AGE

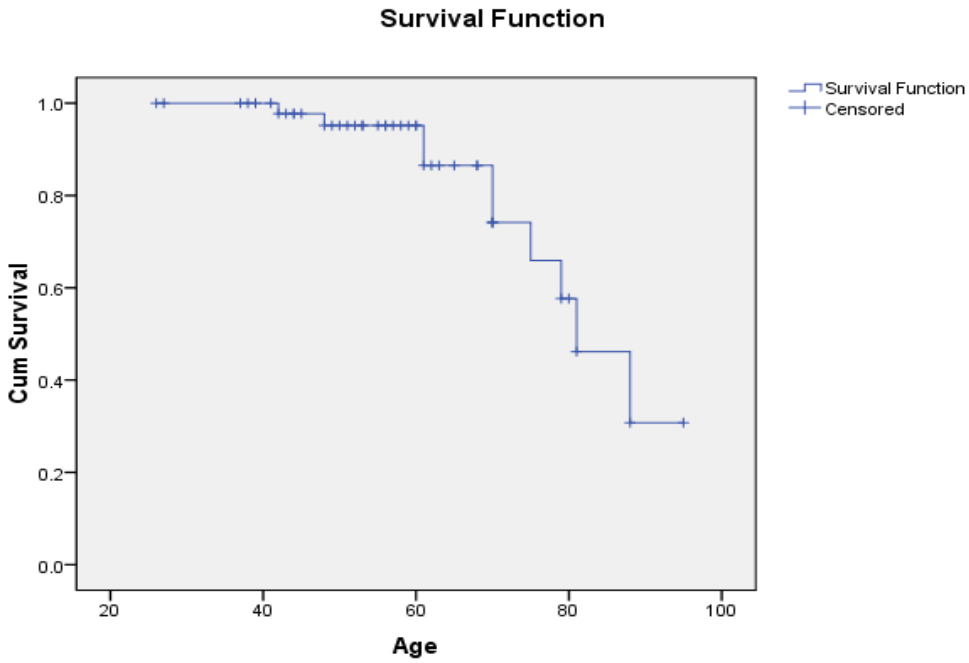
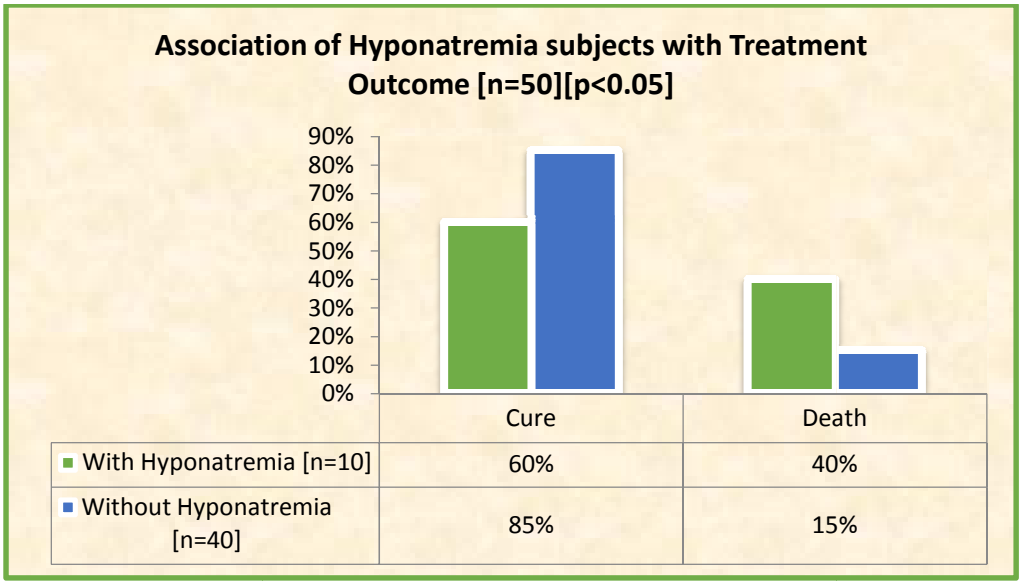


TABLE 25. TREATMENT OUTCOME

	HYPONATREMIA			
Outcome	WITH	WITHOUT	TOTAL	(%)
Cure	6	34	40	80%
Death	4	6	10	20%
TOTAL	10	40	50	

Among the stroke patients, 80% were cured and 20% succumbed to the illness.

CHART 23. TREATMENT OUTCOME

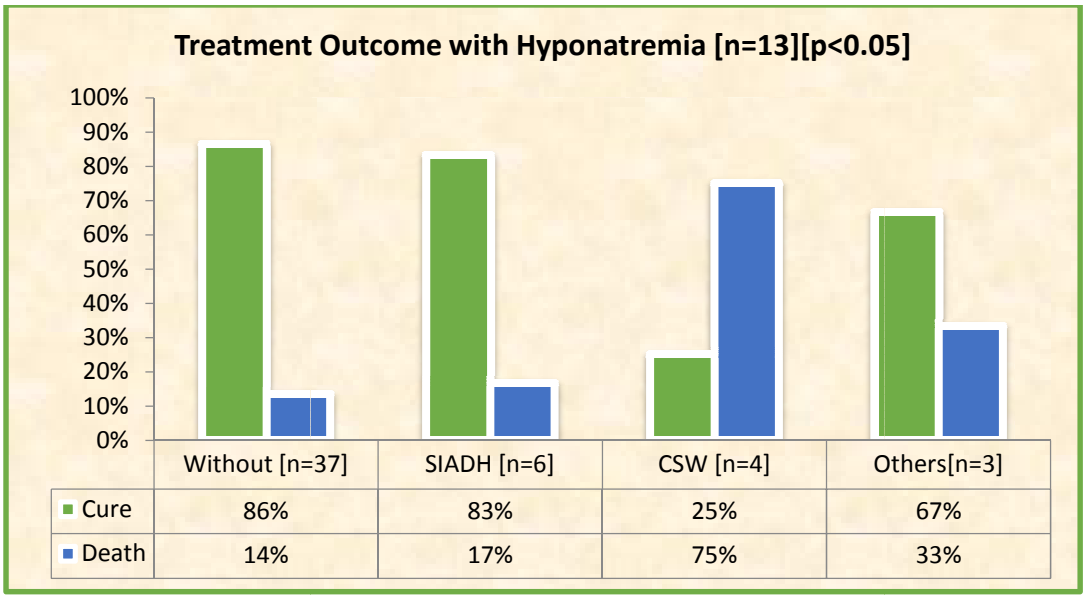


In normonatremic stroke patients, an 85% cure rate and 15% death rate was seen. In hyponatremic patients, there was 60% cure and 40% death. The cure and death rate between the two groups reached a statistical significance. ($p<0.05$)

TABLE 26. TREATMENT OUTCOME OF SIADH vs CSW

	HYPONATREMIA					
Out Come	**Without [n=37]**	**SIADH [n=6]**	**CSW [n=4]**	**Others[n=3]**	**Total**	
Cure	32	5	1	2	40	
Death	5	1	3	1	10	
Total	37	6	4	3	50	

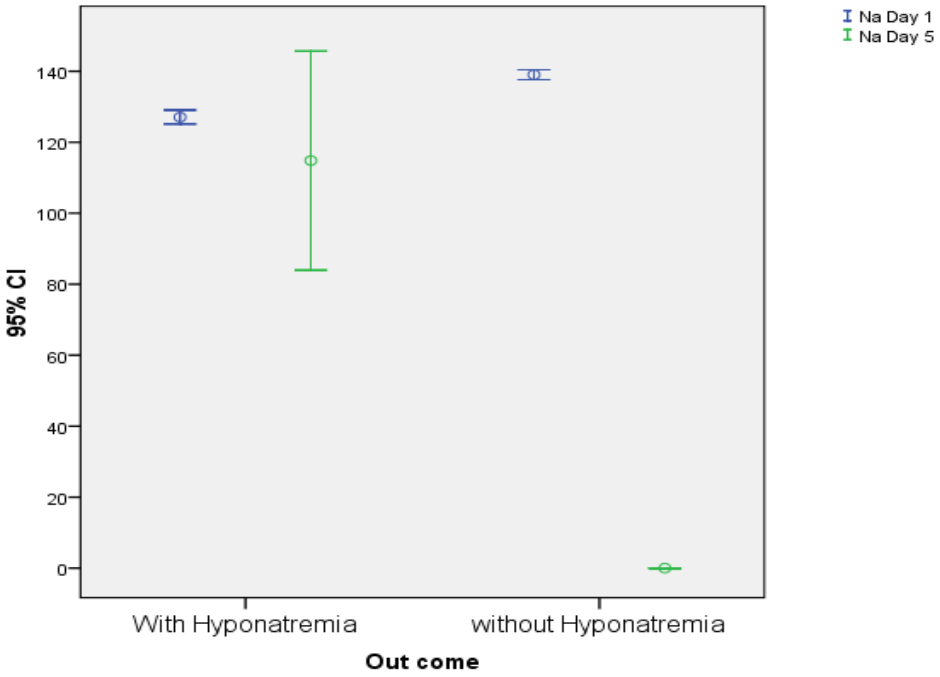
CHART 24. TREATMENT OUTCOME IN SIADH vs CSW



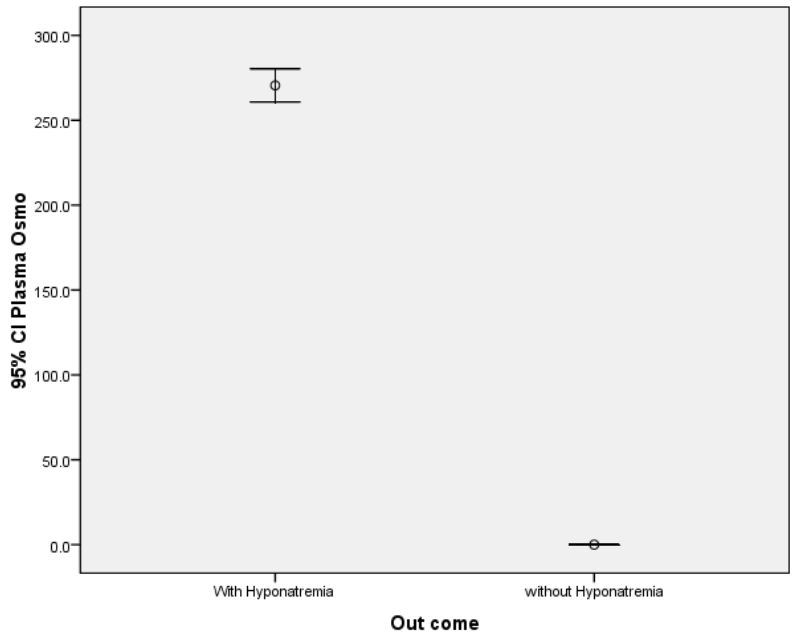
In the SIADH group, 83% were cured of hyponatremia with treatment and 17% patients succumbed. But in the CSW group, only 25% survived and 75% succumbed to the illness. The difference in outcome between the two groups reached statistical significance ($p< 0.05$)

CHART 25. BOX PLOT OF TREATMENT OUTCOME

25A.



25B.



DISCUSSION

DISCUSSION

STROKE

In our study we analysed 50 patients with acute stroke to study the occurrence of hyponatremia.

The majority of stroke patients, about 46%, belonged to the middle age i.e., 40 – 60 years of age.

The mean age of stroke occurrence in males was 56.2 (± 14.5) and that of the females was 66.9 (± 17.3).

This is comparable to the population based study by Dalal et al (42) in Mumbai where the mean age for stroke was 66 years, and in Trivandrum by Sridharan et al (43) where the mean age was 67 years.

The majority of males belonged to 40-60 years age group. The prevalence of stroke in females, however was higher in the 60 to 80 year age group. Thus a higher age stratified prevalence for females was found, which is comparable to the data from the 2008 Mumbai stroke registry (42) where a mean of 63.4 years was recorded for females.

Of the stroke patients in our study group, 76% were male and 24% were female

The prevalence of ischemic stroke was higher (80%), of which 6 patients had lacunar stroke, 5 patients had a massive infarct.

Hemorrhagic stroke was seen in 20%, with 16% having intracerebral bleed and 4% having sub-arachnoid haemorrhage.

This is comparable to the Mumbai stroke registry (42), where 80% of strokes were attributed to be ischemia and 17.7% to haemorrhage.

Accelerated hypertension was the cause of haemorrhage in 4 patients with intra cerebral bleed.

52% had stroke corresponding to the Middle Cerebral Artery territory, 40% with Posterior cerebral artery involvement and 8% with Anterior Cerebral circulation involvement.

HYPONATREMIA

The prevalence of hyponatremia due to cerebral causes was noted in 20% of the acute stroke patients. The prevalence is slightly higher than the study by Kuramatsu et al (44) where prevalence was 15%. Rodrigues B (43) reported a prevalence of 16% and Soiza et al (45) 13.8%.

Of the hyponatremic patients, there was a higher prevalence of SIADH (46%). CSW contributed to 31%. The study by Saleem et al (15) showed the respective prevalences to be 67% and 33%

The prevalence of hyponatremia was the most in the 61-80 year age group (70%).

The prevalence was lower among other age groups and this reached statistical significance ($p<0.05$).

67% of the patients who developed SIADH were of the 61-80 years age group.

All the patients who developed Cerebral Salt Wasting on the other hand belonged to a higher age group (> 65 years). ($p<0.05$)

The trend of hyponatremia prevalence was more in males (70%) but did not reach statistical significance ($p>0.05$)

Both SIADH and CSW showed a higher male prevalence, 67% and 75% respectively.

All the subarachnoid haemorrhage patients in our study developed hyponatremia

Out of the Ischemic stroke patients 18% had hyponatremia.

Hyponatremia was seen in 13% of patients with intracerebral haemorrhage. The most common stroke type seen in hyponatremic patients was ischemic stroke (77%)

Among SIADH patients, 83% had ischemic stroke and 17% had intra cerebral hemorrhage. Saleem et al (15) in his study, showed 35% and 65% respectively.

Among cerebral salt wasting patients, ischemic stroke was found in 50% of patients and SAH was found in 50% patients. In the study by Saleem et al 33% and 67% were the prevalence. (15)

Of the hyponatremia patients, 50% of patients had Middle cerebral territory and 50% had posterior cerebral artery territory involvement.

None of our patients with ACA territory stroke developed hyponatremia.

The majority of patients with SIADH had a posterior circulation stroke, 67%, and 33% had Middle Cerebral Territory stroke.

Saleem et al (15) however, reported 13% and 86% respectively

In CSW, 75% had Middle Cerebral Artery territory involvement and 25% had posterior circulation stroke.

This was comparable with Saleem et al's study (15%) who reported 85% and 15% respectively.

The mean duration of hospital stay was significantly different in patients with hyponatremia 17 days as against 3.73 days in normonatremic patients

The maximum duration of stay seen in one of the hyponatremic patients was 130 days.

A poorer discharge disposition was seen in the hyponatremia group in the study by Rodrigues(43)

In normonatremic stroke patients, an 85% cure rate and 15% death rate was seen.

In hyponatremic patients, there was 60% cure and 40% death. This is similar to the death rate reported by Saleem et al, 40%. (15)

In both the studies, the presence of hyponatremia was found to significantly alter the treatment outcome in patients with stroke ($p<0.05$)

Kuramatsu et al showed that in-hospital mortality was roughly doubled in hyponatremia compared with nonhyponatremia patients (40.9% vs 21.1%), translating into a 2.5-fold increased odds ratio ($P<0.001$). Also, Multivariable analyses identified hyponatremia as an independent predictor of in-hospital mortality ($P=0.037$) (44

In the SIADH group, 83% were cured of hyponatremia with treatment and 17% patients succumbed. But in the CSW group, only 25% survived and 75% succumbed to the illness. CSW was significantly associated with higher death rate. ($p<0.05$)

Survival Curves

The Kaplan Meier analysis showed a significant increase in duration of hospital stay poorer survival in patients with hyponatremia.

Huang W.-Y proved that hyponatremia in the acute stroke stage was associated with higher mortality in hospital (P = .039) and at 3-month (P = .001) and 12-month follow-ups (P = .001), and that it is an independent predictor of 3-year mortality in patients with acute first-ever ischemic stroke.(46)

CONCLUSION

CONCLUSION

- Hyponatremia in the setting of acute stroke occurs in 10-20% patients.
- The prevalence is higher in males and among the middle aged.
- Hyponatremia, attributed to CSW is more common in stroke patients with sub-arachnoid haemorrhage.
- Hyponatremia occurs more with Middle and Posterior cerebral arterial territories involvement.
- SIADH has a higher prevalence than Cerebral Salt Wasting.
- Hyponatremia and especially, cerebral salt wasting predisposes to a longer duration of hospital stay and poorer discharge disposition.
- Hyponatremia, is an independent predictor of short and long term mortality in stroke.
- Cerebral Salt wasting has a poorer short term outcome than SIADH.
- Thus, a clear distinction between the two entities ought to be made and the appropriate treatment be carried out, to reduce the morbidity, short and long term mortality in acute stroke patients with hyponatremia.

SUMMARY

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This study is a cross-sectional study carried out to emphasise the importance of hyponatremia in the setting of a stroke and the impact it can have on the prognosis of the patient. This study was carried out in the premises of Coimbatore Medical College Hospital during a one year period. 50 cases of strokewere selected in random basis and were followed up for occurrence of hyponatremia.

The prevalence of hyponatremia was found to be 20%. The causes of hyponatremia especially Cerebral Salt Wasting and SIADH were studied.

It was found that hyponatremia per se, and Cerebral Salt Wasting in stroke resulted in poorer discharge disposition and longer duration of in-hospital stay and significantly impacted on the short term in-hospital mortality.

The pathophysiology of the two conditions (SIADH and CSW) being entirely different need a completely differing treatment regime and hence the distinction between the two is of utmost importance in neurologic cases with hyponatremia

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ANNEXURES

PROFORMA

DEPARTMENT OF MEDICINE, CMC

NAME :

AGE :

SEX :

IP NUMBER :

ADDRESS :

PHONE NUMBER :

Date of admission

Date of Discharge/ Death

Duration of Hospital stay

PRESENTING COMPLAINTS:

- Weakness
- Seizures
- Giddiness
- Unresponsiveness
- Unsteadiness of gait
- Deviation of angle of mouth

DURATION OF SYMPTOMS :

H/o FEVER/ TRAUMA

PAST HISTORY :

- Prior stroke
- Diabetes mellitus
- Hypertension
- Cardiac disease
- Epilepsy
- Tuberculosis

TREATMENT HISTORY:

FAMILY HISTORY:

ADDICTIONS :

VITALS : Pulse- Rate & Rhythm

Blood Pressure

Respiratory Rate

Temperature

Daily input and output

GENERAL EXAMINATION :

SYSTEMIC EXAMINATION

CENTRAL NERVOUS SYSTEM

Higher Mental Functions: Consciousness

Orientation

Speech

Cranial Nerves

Motor system: Tone

Power

Reflexes

Sensory system

Cerebellar signs

Meningeal signs

GLASGOW COMA SCALE : E V M Total score : /15

CARDIOVASCULAR SYSTEM

Apex Beat

Heart sounds

Murmurs

JVP

RESPIRATORY SYSTEM :

Breath sounds

Added sounds

Percussion

Vocal Resonance

GASTROINTESTINAL SYSTEM

Any tenderness

Liver span

Shifting dullness

General Parameters

- Complete hemogram
- Peripheral Smear
- Random Blood Sugar
- Blood urea
- Serum creatinine
- ECG :
- Chest X-Ray
- SPECIFIC PARAMETERS
- CT scan Brain/ MRI Brain :

- Day of development of Hyponatremia :
- Day 1 of hyponatremia :

  Serum sodium :

  Plasma Osmolality :

  Urine Sodium

  Serum Potassium

  Serum uric acid :

  Serum albumin :

  BUN/ Creatinine

  Hematocrit

  Day 5 of Hyponatremia (safter attempted correction) :

  Serum uric acid

  Serum albumin

  Hematocrit

  Serum potassium

OUTCOME OF THE PATIENT: Death / Recovery and discharge

CONSENT FORM

You, Shri./ Smt./ Kum. _____, aged ____ years, S/o / D/o / W/o _____, residing at _____ _____ are requested to be a participant in the research study titled *"Hyponatremia in stroke: Cerebral Salt Wasting versus Syndrome of Inappropriate Anti diuretic hormone secretion*"conducted by Dr. Mithra Prasad., one of the post graduate trainees in the Dept. of General Medicine, Govt. Coimbatore Medical College and Hospital, Coimbatore. You are eligible for the study as per the inclusion criteria. You can ask her any question or seek from her any clarifications about the study which you may have before agreeing to participate in the study.

TOPIC OF THE RESEARCH

"Hyponatremia in stroke: Cerebral Salt Wasting versus Syndrome of Inappropriate Anti-Diuretic Hormone secretion"

PURPOSE OF RESEARCH

Hyponatremia is one of the most common abnormalities in patients with stroke and is also one of the most easily missed or mistreated electrolyte abnormality. Hyponatremia can significantly influence the outcome of stroke and thus warrants a proper correction. Both SIADH and cerebral salt wasting should be differentiated since treatment modalities differ.

PROCEDURES INVOLVED IN THE STUDY

Properly elicited medical history pertaining to the patient's complaints.

Detailed general and systemic examination as guided by the medical history.

Blood and imaging investigations as guided by the clinical diagnosis.

Treatment with standard protocol currently followed in our hospital.

Continued follow-up of patient in the intensive medical care unit and the ward

Recording all the above variants/events into the database and analyzing them by statistical methods to arrive at our objectives.

DECLINING FROM PARTICIPATION

You are hereby made aware that participation in this study is purely voluntary and honorary, and that you have all the rights to decline from participating in it.

PRIVACY AND CONFIDENTIALITY

You are hereby assured that your privacy is respected. Any information about you or provided by you during the study will be kept strictly confidential.

AUTHORIZATION TO PUBLISH RESULTS

Results of the study may be published for scientific purposes and/or presented to scientific groups. In any case, neither will your identity be revealed nor will your privacy be breached.

STATEMENT OF CONSENT

I, _____, do hereby volunteer and consent to participate in this study being conducted by Dr. Mithra Prasad I have read and understood the consent form (or) it has been read and explained to me thoroughly. I am fully aware of the study details as well as aware that I may ask questions to him at any time.

Signature / Left Thumb Impression of the patient

Station: Coimbatore

Date:

Signature / Left Thumb Impression and Name of the witness

Station: Coimbatore

Date:

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவ துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவி **மரு. மித்ரா பிரசாத்** அவர்கள் மேற்கொள்ளும் **"பக்கவாதத்தில் உப்பு சத்து (சோடியம்) குறைபாடு : தேவைக்கு அதிகமான அளவு ADH ஹார்மோன் சுரத்தல் காரணத்தாலா அல்லது மூளையில் உப்பு சத்து தேய்மானத்தினாலா? "** பற்றிய ஆய்வில் செய்முறை மற்றும் அனைத்து விளக்கங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடனும், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னைப் பற்றிய அனைத்து விவரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம்

தேதி கையொப்பம் / ரேகை

MASTER CHART

NORMONATREMIC GROUP (n=37)

S.No	IP NO.	Age	Sex	Stroke type	Territory	Side	Serum Sodium	Duration of hospital stay	Outcome
1	48839	39	1	1	2	2	138	3	1
2	50299	55	1	1	2	1	136	2	1
3	53341	44	1	1	3	1	134	4	1
4	52039	38	1	1	2	2	141	5	1
5	52118	26	2	1	2	1	142	4	1
6	52725	27	1	1	1	2	135	4	1
7	55800	53	1	1	2	2	138	2	1
8	55365	52	1	1	3	2	136	3	1
9	57513	42	1	1	2	1	145	4	1
10	59062	37	1	1	2	1	143	5	1
11	59105	53	1	2	2	1	139	4	1
12	59060	43	1	1	3	2	138	10	1
13	56628	68	1	1	3	1	146	8	1
14	59238	41	1	1	2	2	143	3	1
15	60730	70	1	1	3	2	148	5	1
16	60877	48	1	2	3	1	135	3	2
17	61758	60	1	1	3	3	141	8	1
18	61144	48	1	2	2	2	141	3	1
19	57889	65	1	1	3	1	140	4	1
20	52269	88	2	2	3	3	141	2	2
21	55535	50	1	1	2	1	135	3	1
22	51122	61	1	1	3	2	136	3	1
23	54356	56	1	1	3	1	136	4	1
24	53741	70	2	1	2	1	131	4	2
25	60778	42	1	2	3	3	141	3	2
26	60999	56	1	1	2	1	138	2	1
27	55941	81	2	1	2	1	136	5	1
28	59108	59	2	1	2	1	138	1	1
29	53456	60	1	1	2	1	146	5	1
30	60998	70	1	1	2	2	142	4	1
31	59244	61	2	1	1	3	130	2	**2**
32	53334	58	1	1	3	1	141	2	1
33	55567	44	1	1	1	2	140	4	1
34	60456	49	1	2	2	1	138	2	1
35	50334	95	1	1	2	1	132	3	1
36	60948	57	2	1	1	3	144	1	1
37	60105	88	1	2	2	1	140	4	1

HYPONATREMIC GROUP (n=13)

S.No	IP NO.	Age	Sex	Stroke type	Territory	Side	Na Day 1	Na Day 5	Serum K	Day of hyponatremia development	Plasma Osmo	Volume Status	UrineSodium	Uric acid 1	Uric acid 5	BUN/ Creatinine	HCT 1	HCT 5	Albumin 1	Albumin 5	SIADH/ CSW	Duration of hospital stay	Outcome
1	48887	79	1	2	3	1	117	144	4.8	1	248.8	3	42	3	4.8	7.45	37.8	41	3.1	3	1	5	2
2	60874	68	1	1	3	2	128	137	4.4	3	265	1	37	2.2	4.7	17.3	35.4	40	3.2	4.6	1	6	1
3	52345	62	1	3	2	1	128	131	6.2	4	268	2	32	3.1	2.9	32	52	44	4.1	3	2	6	1
4	60045	45	1	1	3	1	129	133	3.7	5	267	3	26		6	8.125	38	42	2.5	4.1	1	12	1
5	56678	63	1	1	3	3	126	136	4	9	265	1	29	2	4.9	12.13	32.7	34	4	4.4	1	12	1
6	53835	80	2	1	2	3	127	132	3.7	5	284		14			3					3	18	1
7	54756	79	2	1	2	1	129	133	5	1	274	3	23	3.3	5.2	18	49.2	48	2.1	2.6	1	5	1
8	55714	51	2	1	2	1	127	136	4.4	1	255	1	38	2.1			32.5	33	3.4	3.6	1	4	1
9	52113	61	1	1	2	1	128	134	6	5	269	2	27.3	2.6	2.5	19.3	55.7	50	4.6	3.9	2	130	2
10	53929	75	1	3	3	3	128		3.9	2	248	2	33	3	3.4	21.1	48	33	4.1	3.3	2	8	2
11	62655	70	2	1	2	2	130	136	3.62	2	299		46.5			18.8					3	10	1
12	57361	70	1	1	2	3	129	141	2.8	3	299										3	4	2
13	59149	81	2	1	2	1	126		5.8	1	275	2	25	2.5		37.2	48		5.1		2	1	2

KEY TO MASTER CHART

S.No.	-	Serial Number
IP No.	-	Inpatient Number
Age	-	(in years)
Sex	-	1- Male
		2- Female
Stroke type	-	1-Ischemic stroke
		2-Intracerebral hemorrhage
		3-Sub-arachnoid hemorrhage
Stroke territory	-	Vascular territory involved in stroke
		1- Anterior cerebral Artery
		2- Middle cerebral Artery
		3- Posterior cerebral Artery
Side	-	Side of cerebral involvement
		1- Right
		2- Left
Serum Sodium	-	(Units - meq/L)
Na	-	Sodium
Serum K	-	Serum Potassium (Units - meq/L)
Plasma Osmolality	-	(Units- mosm /kg)
Volume status	-	ECF volume
		1- Increased
		2- Decreased
		3- Normal
Urine sodium	-	(units meq/L)

Uric Acid	-	(Units mg/ dl)
		Uric acid 1-day 1 value of uric acid
		Uric acid 5-day 5 value of uric acid
BUN /Creatinine	-	(Units mg/ dl)
Hct	-	Hematocrit (units - %)
		Hct-1 - day 1 hematocrit
		Hct -5 - day 5 hematocrit
Albumin	-	(Units g/dl)
		Albumin 1 - day 1 albumin
		Albumin 5 - day 5 albumin
SIADH	-	Syndrome Of Inappropriate Anti-diuretic Hormone secretion
CSW	-	Cerebral Salt Wasting
Duration of Hospital stay	-	(In days)
SIADH/CSW	-	1-SIADH
		2-CSW
Outcome	-	1-Cure
		2-Death